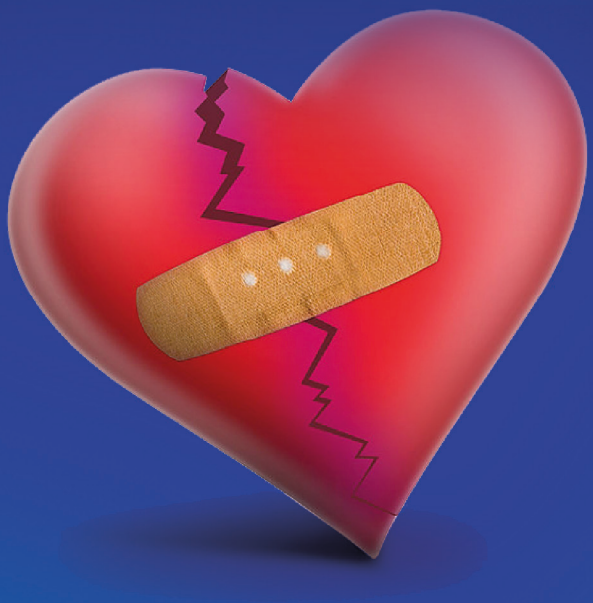
Decision Making in Patients Undergoing Coronary Artery Revascularization

A New Era in Clinical Trial Design and Evidence-Based Practice



Milan Milojevic

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Milan Milojevic

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Decision Making in Patients Undergoing Coronary Artery Revascularization

A New Era in Clinical Trial Design and Evidence-Based Practice

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.Dr. R.C.M.E. Engels

and in accordance with decision of the Doctorate Board.

The public defence shall be held on
Friday 28th of June 2019 at 13:30 hours

By

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For my dearest family

“I don’t care that they stole my idea. I care that they don’t have any of their own.”

– Nikola Tesla.

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Chapter 1

General Introduction

GENERAL INTRODUCTION

Coronary artery disease (CAD) remains the single leading cause of death in Europe, accounting for more than 860,000 deaths annually in men (19%) and 875,000 deaths annually in women (20%) (Figure 1) despite massive resources dedicated to research and treatment (1). With an estimated hospital admission rate of approximately 19.5 per 1000 patients and the average length of stay of 8.7 days, the treatment of CAD also represents a significant disease burden with severe economic and social impact (2).

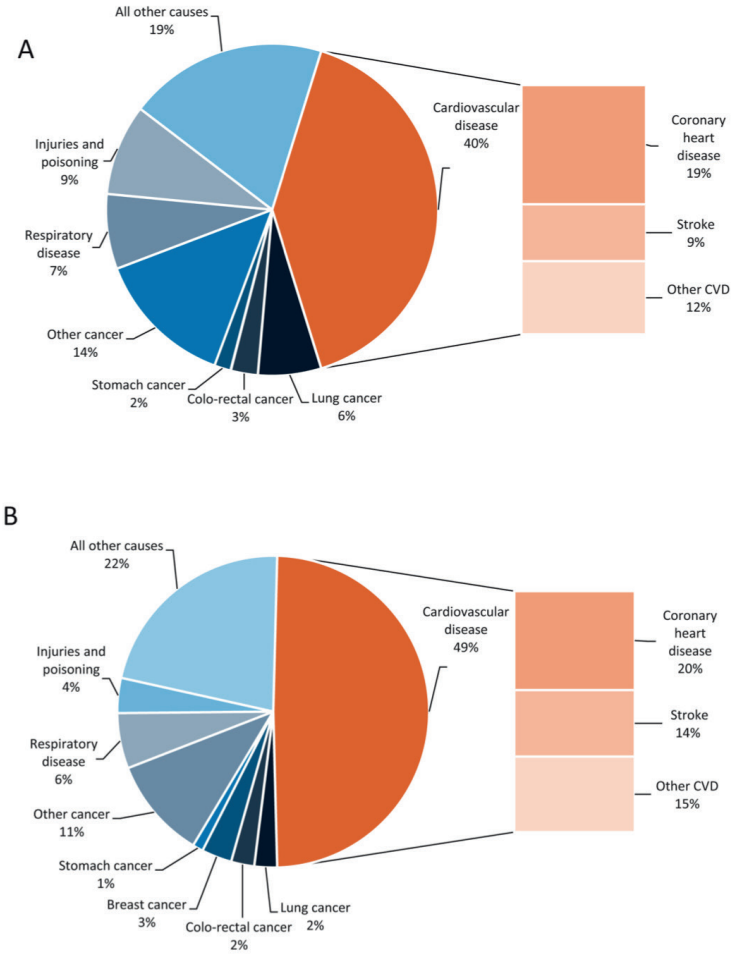


Figure 1. Causes of death in Europe (A) among men and (B) women. Source: WHO Mortality Database 2016 (1). Note: no data available for Andorra.

In general, all patients with CAD require lifestyle modification and lifelong optimal medical therapy to improve angina symptoms, decrease the progression of the disease, and reduce the risk of death, myocardial infarction and heart failure (3, 4). The decision to proceed with revascularization by either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) is reserved for patients with disabling symptoms despite intensive medical therapy, those in whom intensive medical treatment is not well tolerated or want to increase their physical activity level, and patients with complex coronary anatomy (e.g. left main coronary disease and multivessel coronary disease) for which myocardial revascularization has a clearly establish survival benefit over medical therapy (5).

It should be noted that the use of PCI and CABG procedures still remarkably varies across European countries (Figure 2). Cross-country variability reflects different clinical practice on a national level as a consequence of the variation in reimbursement policy, health-care infrastructure, and the health status of the nation (6), but also suggests a lack of high-quality evidence to identify the target population of patients who will undoubtedly benefit from the specific treatment with PCI or CABG:

"It's not hard to make decisions once you know what your values are."

Roy E. Disney

Ideally, the choice between CABG and PCI should be based on data accumulated from clinical trials, and patient preferences when appropriate (7, 8). However, myocardial revascularization with both CABG and PCI is rapidly evolving. PCI is undergoing improvements in long-term safety and efficacy of coronary stents, while CABG is improving by better perioperative care, use of more arterial grafts, and adherence to secondary prevention medications (9, 10). Moreover, new treatment strategies for both PCI and CABG include the use of functional revascularization assessment to avoid unnecessary revascularization. These continually evolving treatment strategies have led to a continuous debate on which of these two procedures provides the best care among various subsets of patients (11).

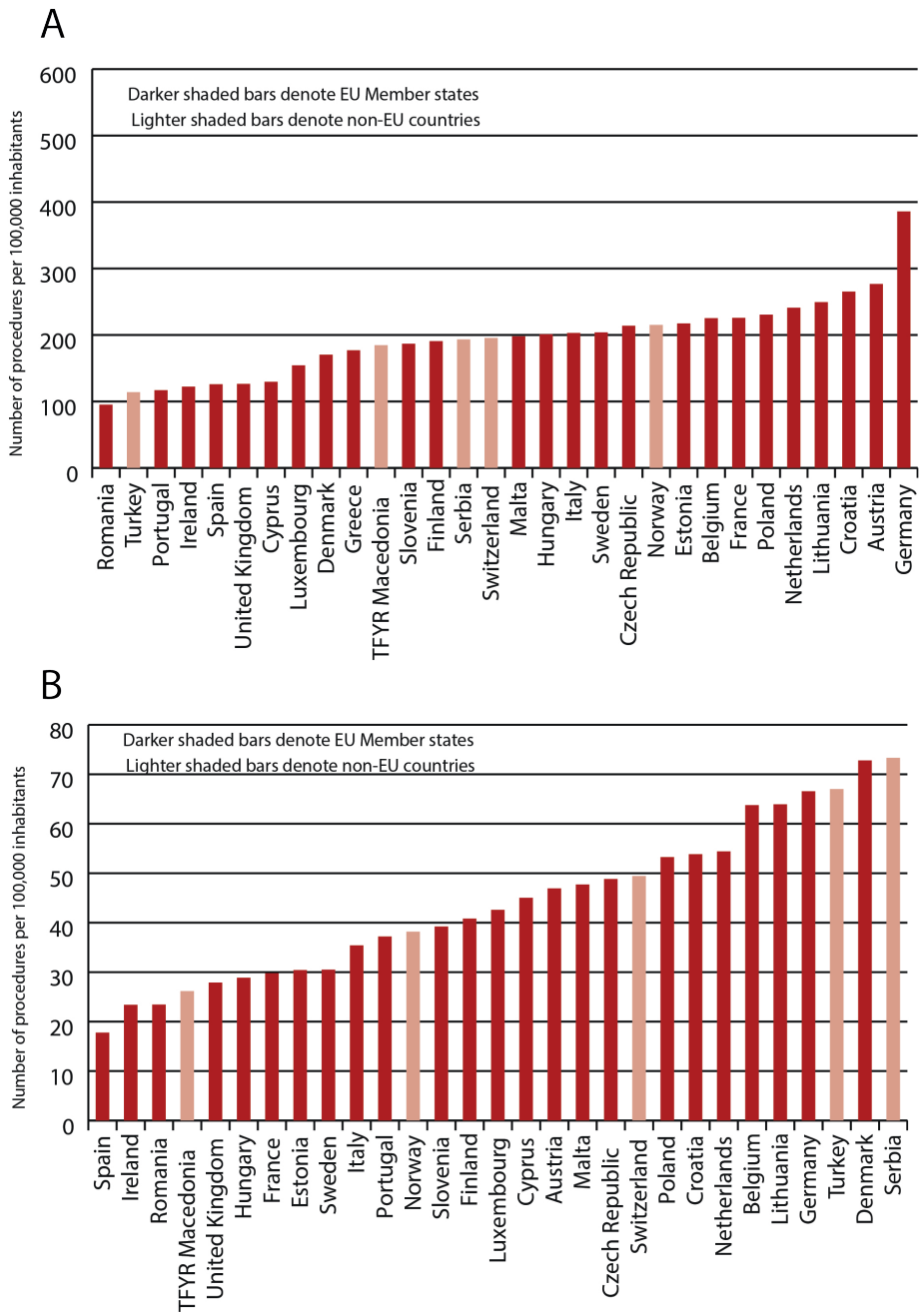


Figure 2. Rates of percutaneous coronary intervention (A) and coronary artery bypass grafting **(B)** in Europe in 2017 (2).

Despite the recent developments in PCI practice, with the introduction of drug-eluting stents, it remains to be determined whether the efficacy and relative safety of PCI has improved compared to contemporary outcomes of CABG. Therefore, to identify the most appropriate revascularization modality for a particular patient, more high-quality data from modern clinical practice are needed. Moreover, for most patients with complex CAD, the most critical determinants of long-term survival are age, diabetes mellitus, chronic kidney disease, left ventricular ejection fraction, and the severity and location of coronary lesions, but it remains mostly unclear how contemporary PCI and CABG compare in these particular subsets.

The development and update of clinical guidelines are based on an evaluation of the latest data from contemporary clinical studies. Modern clinical practice emphasizes the value of evidence-based medicine for daily activities as one of the ultimate requirements for best patient care. Clinical guidelines are aimed at helping medical practitioners, and health-care authorities bridge the gap between the best available evidence and local practice, treatment costs, and patient choice (12). More importantly, changes in clinical practice depend on the dissemination and evaluation of clinical guidelines, the existence of which should be vigorously pursued supported through all available informal and formal informational channels:

"Guidelines do not implement themselves."

Marilyn J. Field and Kathleen N. Lohr, 1992.

The focus of this thesis is on the management of patients with complex CAD by means of PCI or CABG, to improve outcomes and potentially lead to an individualized treatment selection based on the risk profile of a particular patient. Moreover, our clinical research focuses on an integrated care model to incorporate decision to proceed with CABG in conjunction with established pillars of i) the use of optimal surgical techniques, and ii) aggressive risk-factor modification through guideline-directed pharmacological therapies and lifestyle modifications.

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Chapter 2

Aims and Outline

AIMS

The aims of this thesis are to study the comparative effectiveness of coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI) and to critically assess the available evidence, resulting in practical recommendations for improved treatment decision-making in patients needing myocardial revascularization.

More specifically, the following research questions are addressed:

1. What is the current status of surgical myocardial revascularization?

2. What are the outcomes of contemporary CABG versus PCI?

3. Is bypass surgery the preferred revascularization strategy over PCI in patients with specific clinical profiles?

4. How do globalization and use of the composite outcomes affect the interpretation of clinical trial results?

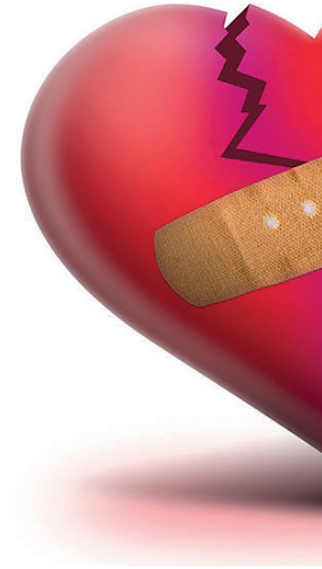
5. How to improve health care quality, patient outcomes, and costs with the current body of evidence in cardiac surgery; development of evidence-based clinical practice guidelines.

OUTLINE

Part 1 of this thesis focuses on the contemporary indications, treatment strategies and outcomes of surgical revascularization. The 40-year clinical outcome and life expectancy after venous CABG surgery is established. Moreover, the feasibility and safety of a Heart Team approach to myocardial revascularization and the long-term results are studied in real life settings.

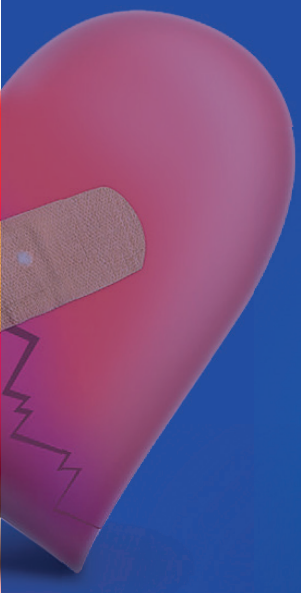
Part 2 aims to investigate the most appropriate revascularization strategy in specific patients with complex coronary artery disease. We compare the long-term outcomes of CABG versus PCI in patients with and without diabetes, chronic kidney disease, and patients with multivessel and/or left main coronary disease. The main focus of this section is to investigate the outcomes that are of critical importance for decision-making including mortality, stroke, myocardial infarction and need for repeat revascularization. Furthermore, a new hierarchical approach is applied to test the primary composite endpoint to capture meaningful clinical effects of CABG versus PCI. A specific analysis of differences in practice patterns among countries enrolled in clinical trials is performed, highlighting the recommendations for the design of future studies and identify interventions for improvement in particular countries.

Part 3 examines the adherence to guideline-directed medical therapy following myocardial revascularization in the landmark clinical trials and provides evidence-based recommendations for perioperative medication management in patients undergoing cardiac surgery to improve short- and long-term prognosis.



Part 1

Current Practice in Bypass Surgery



Chapter 3

Life-long clinical outcome after the first myocardial revascularization procedures: 40-year follow-up after coronary artery bypass grafting and percutaneous coronary intervention in Rotterdam

Milojevic M, Thuijs DJFM, Head SJ, Domingues CT, Bekker MWA, Zijlstra F, Daemen J, de Jaegere PPT, Kappetein AP, van Domburg RT, Bogers AJ.

Interact Cardiovasc Thorac Surg. 2019; In press.

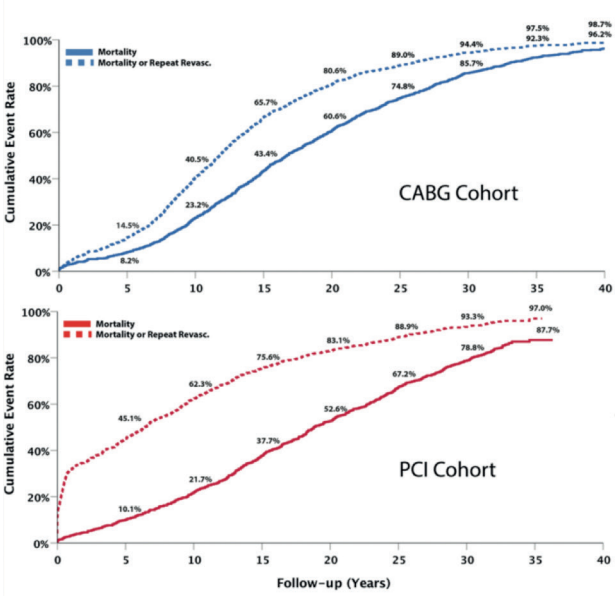
ABSTRACT

AIM: Our goal was to evaluate the outcomes of the first patients treated by venous coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI) with balloon angioplasty at a single centre who have reached 40 years of life-long follow-up.

METHODS AND RESULTS: We analyzed the outcomes of the first consecutive patients who underwent (venous) CABG (n=1041) from 1971 to 1980 and PCI (n=856) with balloon angioplasty between 1980 and 1985. Follow-up was successfully achieved in 98% of patients (median 39 years, range 36-46) who underwent CABG and in 97% (median 33 years, range 32-36) of patients who had PCI. The median age was 53 years in the CABG cohort and 57 years in the PCI cohort. A total of 82% of patients in the CABG group and 37% of those in the PCI group had multivessel coronary artery disease. The cumulative survival rates at 10, 20, 30 and 40 years were 77%, 39%, 14% and 4% after CABG, respectively, and at 10, 20, 30 and 35 years after PCI were 78%, 47%, 21% and 12%, respectively. The estimated life expectancy after CABG was 18 years and 17 years after the PCI procedures. Repeat revascularization was performed in 36% and 57% of the patients in the CABG and PCI cohorts, respectively.

CONCLUSIONS: This unique life-long follow-up analysis demonstrates that both CABG and PCI were excellent treatment options immediately after their introduction as the standard of care. These procedures were lifesaving, thereby indirectly enabling patients to be treated with newly developed methods and medical therapies during the follow-up years.

VISUAL ABSTRACT



Key question

What was the life-long outcome after either venous CABG or PCI with the balloon angioplasty revascularization procedure?

Key finding(s)

Life expectancy after CABG was 18 years and that after PCI was 17 years; repeat revascularization rates were 36% and 57%, respectively.

Take-home message

Although revascularization evolved dramatically, CABG and PCI seemed to be durable treatments after they were introduced into daily practice.

INTRODUCTION

Since the introduction of the modern coronary artery bypass grafting (CABG) with venous and internal mammary artery (IMA) grafts in 1964 and percutaneous coronary intervention (PCI) with balloon angioplasty in 1977, these procedures have been performed extensively to treat coronary artery disease (CAD) worldwide (1, 2). According to results from the Eurostat Database, coronary revascularization is one of the most common major hospital interventions performed in the European Union with an average rate of 258 per 100,000 inhabitants (3).

Advancements in both techniques and guideline-directed medical therapies have improved life expectancy and quality of life (4). However, although long-term follow-up is available (5, 6), data on the life-long outcomes after CABG and PCI are still not published. Despite revascularization treatment has significantly changed and improved since its introduction, it is essential to establish the outcome of the first routinely treated patients, because life-long results (i) provide an opportunity to establish risk factors that show late sequelae, (ii) lend credibility for future studies and iii) provide more insight into the real prognosis of patients. Therefore, we determined the outcome from life-long follow-up after the first CABG and PCI procedures.

METHODS

Study population

The study population and methods were described previously in detail (5, 6). Briefly, the CABG population of this study comprised 1041 consecutive patients who underwent a first elective isolated coronary surgery with venous grafts between 1971 and 1980 at the Erasmus Medical Center. During that period, internal mammary artery (IMA) grafts were not yet used at our institution. Indications for surgical revascularization were stable or unstable angina despite intensive pharmacological therapy. The intent was to achieve complete revascularization of significantly obstructed proximal coronary segments of the major arteries. Patients with any previous or concomitant cardiac surgical procedures were excluded from the current study.

The PCI cohort comprised 856 consecutive patients who underwent a first balloon angioplasty procedure between 1980 and 1985 at the Erasmus Medical Centre. Seventy-six patients were treated for acute myocardial infarction (MI), and

other patients had either stable or unstable angina. At that time, all patients had intensive pharmacological therapy with beta-blockers, calcium channel blockers and nitrates, with intravenous heparin for unstable patients. Before the PCI procedure, 250 mg of acetylsalicylic acid and 100 mg of unfractionated heparin were administered intravenously, following additional boluses of 50 mg per hour. At hospital discharge, conventional treatment included acetylsalicylic acid of 500 mg daily for at least 6 months as well as a high dose of nifedipine.

The primary end point of this study was all-cause death. Secondary end points were repeat revascularization and a composite of death and repeat revascularization. Patients with multivessel disease were defined as having 2or 3-vessel disease. Left ventricular (LV) dysfunction was defined as an ejection fraction < 50%. For this observational study, patients were not subject of additional treatment or diagnostic procedures; neither was any mode of behaviour imposed other than as part of their regular treatment. Therefore, according to Dutch law at that time, written informed consent for a patient to be enrolled in this study was not required. This study was conducted according to the privacy policy of the Erasmus Medical Centre and to the Erasmus Medical Centre regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki.

Follow-up

Patients who had CABG or PCI were followed from the date of the index procedure until the time of death or the time of the last available follow-up. Data regarding death or repeat revascularization were updated at 12 months after the index procedure and every 5 to 7 years after that, by reviewing hospital and general practitioner records and the civil registry or by telephone interviews with patients/family members. Follow-up was complete in 98% of patients who had CABG and 97% of patients who had PCI who were recruited in the cohorts. The survival status of 22 patients who had CABG and 25 patients who had PCI could not be retrieved because they had emigrated, and these patients were censored at the date of the last follow-up. Since the early 1980s, all data were prospectively entered into a dedicated database.

Statistical analysis

No statistical comparisons were performed between PCI and CABG because the entry criteria differed as to inclusion period, clinical presentation and the complexity of the CAD.

Data are presented using descriptive statistics, as a percentage, count of sample

size or median ± interquartile range (IQR). Cumulative time-to-event Kaplan-Meier estimates were used to assess the clinical outcomes after PCI at 35 years and CABG at 40 years among overall cohorts and according to the number of diseased vessels. Life expectancy (LE) after CABG and PCI was calculated from the area under the Kaplan-Meier curves (5). The expected survival in a reference population was calculated using ageand gender-specific mortality data from the Netherlands during the study period (www.cbs.nl) and was compared with survival rates of patients after CABG and PCI. Multivariable Cox proportional hazards models were constructed to identify independent prognostic factors for very long-term mortality rates using baseline characteristics: age, gender, history of smoking, diabetes, hypertension, dyslipidaemia, 3-vessel disease and LV dysfunction. A 2-sided p-value of <0.05 was considered to be statistically significant. Analyses were performed using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY USA).

RESULTS

Coronary artery bypass grafting cohort

The median age was 53 years (interquartile range (IQR), 48-58 years), and 88% were male (Table 1). A total of 9% had diabetes, 31% had a diagnosis of LV dysfunction and the majority 73% had multivessel disease.

Median follow-up was 39 ± 2 years (range 36-46), during which 979 deaths occurred. Cumulative survival rates were 77% at 10 years, 39% at 20 years, 14% at 30 years, and 4% at 40 years (Fig. 1). Estimated LE was 18 years.

The number of diseased vessels was strongly correlated with higher mortality rates (Fig. 2A). The survival rates in patients with 2-vessel disease were significantly higher compared to those in patients with 3-vessel disease at 10 years (82% vs 71%), 20 years (46% vs 28%), 30 years (16% vs 9%) and 40 years (4% vs 2%). Independent predictors of the 40-year mortality rate were age, diabetes, hypertension, LV dysfunction and 3-vessel disease (Table 2).

A total of 668 repeat revascularizations were performed in 375 patients (36%). Of those patients who required repeat procedures, repeat CABG procedures were needed in 315 (84%) patients, and 164 patients underwent at least 2 repeat revascularizations (Fig. 3). The hazard of repeat revascularization was highest 7 to 13 years after the initial procedure (Fig. 4A). Freedom from death or repeat

revascularization was 60% at 10 years, 19% at 20 years, 6% at 30 years and 1% at 40 years (Fig. 1).

Table 1. Baseline characteristics.

Characteristic	CABG (n=1041)	PCI (n=856)
Age, IQR	53.0 (47.7-58.4)	56.9 (50.4-62.7)
Range	28-70	22-80
Male	915 (87.9)	684 (79.9)
Smoking (history)	589 (57.8)	497 (58.0)
Diabetes	82 (8.6)	99 (11.6)
Hypertension	224 (21.6)	338 (40.5)
Dyslipidemia	232 (22.4)	241 (27.4)
LV dysfunction	274 (31.4)	104 (16.6)
Normal (≥50%)	601 (68.6)	523 (83.4)
Moderate (30-49%)	247 (28.3)	97 (15.5)
Low (<30%)	27 (3.1)	7 (1.1)
Vessel disease		
1-vessel	192 (18.4)	543 (63.4)
2-vessel	320 (30.7)	198 (23.6)
3-vessel	445 (42.7)	97 (11.8)
Left main	84 (8.1)	11 (1.3)

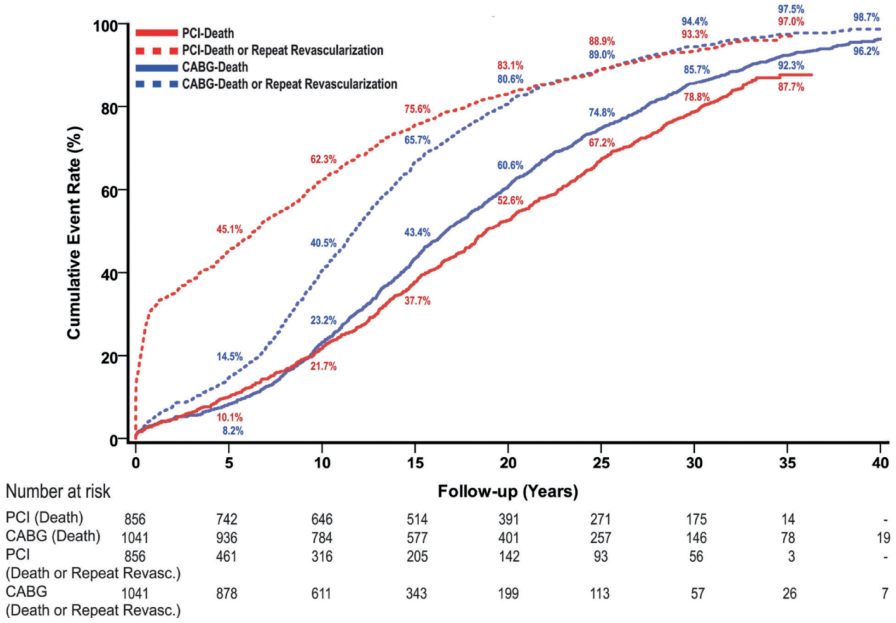
Numbers are presented as n (%) or as median with IQR. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LV, left ventricular; IQR, interquartile range.

Percutaneous coronary intervention cohort

The median age at the time of PCI was 57 years (IQR, 50-63 years), and 80% were men (Table 1). Diabetes was present in 12%, LV dysfunction in 17%; the majority (63%) had 1-vessel disease.

Mean follow-up was 33 ± 1 years (range 32-36), during which 707 deaths occurred. Cumulative survival rates were 78% at 10 years, 47% at 20 years, 21% at 30 years and 12% at 35 years (Fig. 1). Estimated LE was 17 years.

The number of diseased vessels at baseline was an essential determinant of an increase in mortality rates (Fig. 2B). Cumulative survival rates were markedly higher among patients with 2-vessel disease versus those with 3-vessel disease at 10 years (78% vs 56%), 20 years (40% vs 31%), 30 years (17% vs 9%) and 35 years (10% vs 5%). Independent predictors of the 35-year mortality rate were age, history of smoking, hypertension, LV dysfunction and 3-vessel disease (Table 2).



Number at risk

PCI (Death)	856	742	646	514	391	271	175	14	-
CABG (Death)	1041	936	784	577	401	257	146	78	19
PCI (Death or Repeat Revasc.)	856	461	316	205	142	93	56	3	-
CABG (Death or Repeat Revasc.)	1041	878	611	343	199	113	57	26	7

Figure 1. Survival and event-free survival estimates after CABG and PCI. Values are Kaplan-Meier event rates. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; Revasc., revascularization.

Table 2. Independent predictors of long-term mortality.

	HR (95% CI)	*P*-Value
CABG cohort (n=1041)		
Age (per 5-year increments)	1.30 (1.23-1.37)	<0.001
Male	1.22 (0.97-1.54)	0.092
Smoking (history)	0.91 (0.78-1.05)	0.21
Diabetes	1.31 (1.01-1.70)	0.042
Hypertension	1.24 (1.04-1.48)	0.018
Dyslipidemia	0.95 (0.80-1.14)	0.60
Three-vessel disease	1.17 (1.08-1.27)	<0.001
LV dysfunction	1.79 (1.53-2.10)	<0.001
PCI cohort (n=856)		
Age (per 5-year increase)	1.40 (1.31-1.48)	<0.001
Male	1.01 (0.81-1.27)	0.93
Smoking (history)	1.29 (1.08-1.55)	0.005
Diabetes	1.19 (0.88-1.61)	0.25
Hypertension	1.20 (1.01-1.44)	0.039
Dyslipidemia	0.86 (0.69-1.07)	0.17
Three-vessel disease	1.53 (1.19-1.96)	0.001
LV dysfunction	1.38 (1.09-1.75)	0.007

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; LV, left ventricular; PCI, percutaneous coronary intervention.

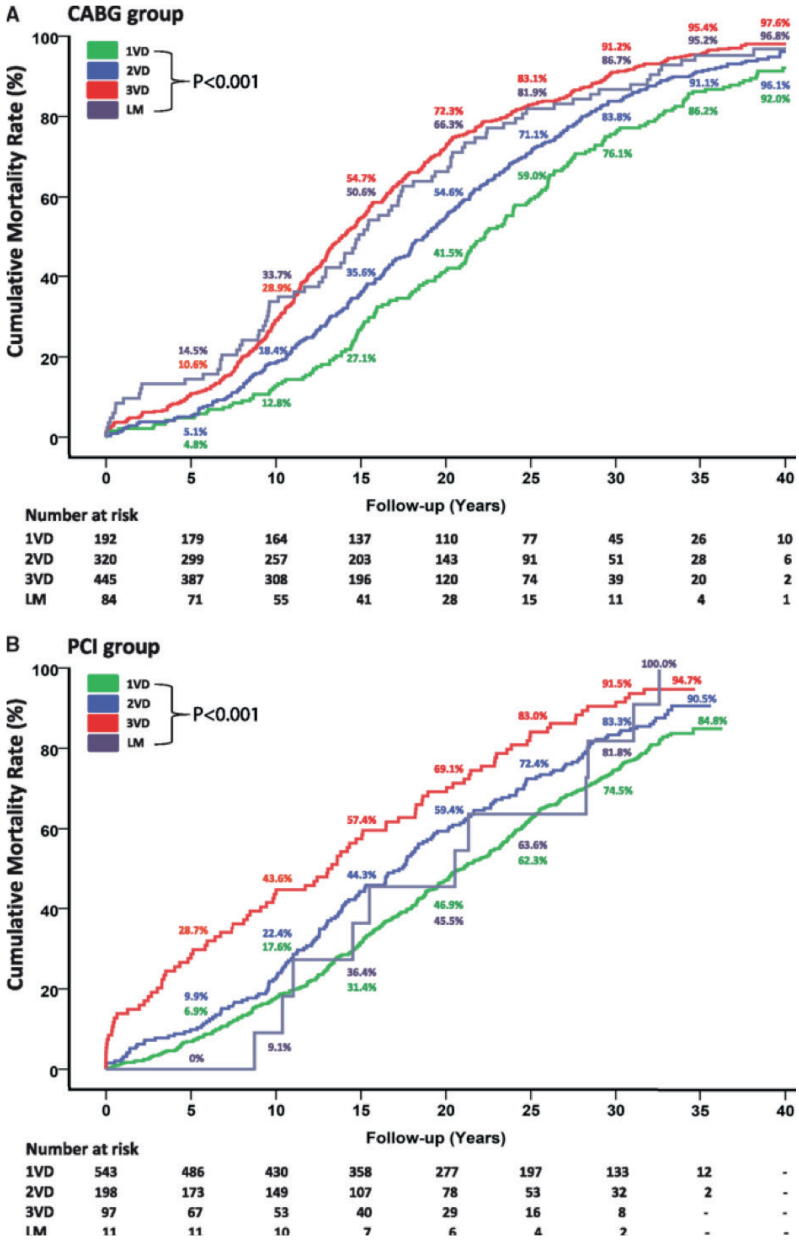


Figure 2. Death after CABG **(A)** and PCI **(B)** according to the number of diseased vessels. Values are Kaplan-Meier event rates. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LM, left main; VD, vessel disease.

A total of 831 repeat revascularization procedures were performed in 484 patients (57%). A CABG procedure was performed in 325 of these patients (67%), and at least 2 repeat revascularizations were required in 201 patients during the follow-up period (Fig. 3). The hazard of repeat revascularization reached its peak during the first year after the initial procedure (Fig. 4B). Freedom from death or repeat revascularisation was 38% at 10 years, 17% at 20 years, 7% at 30 years and 3% at 35 years (Fig. 1).

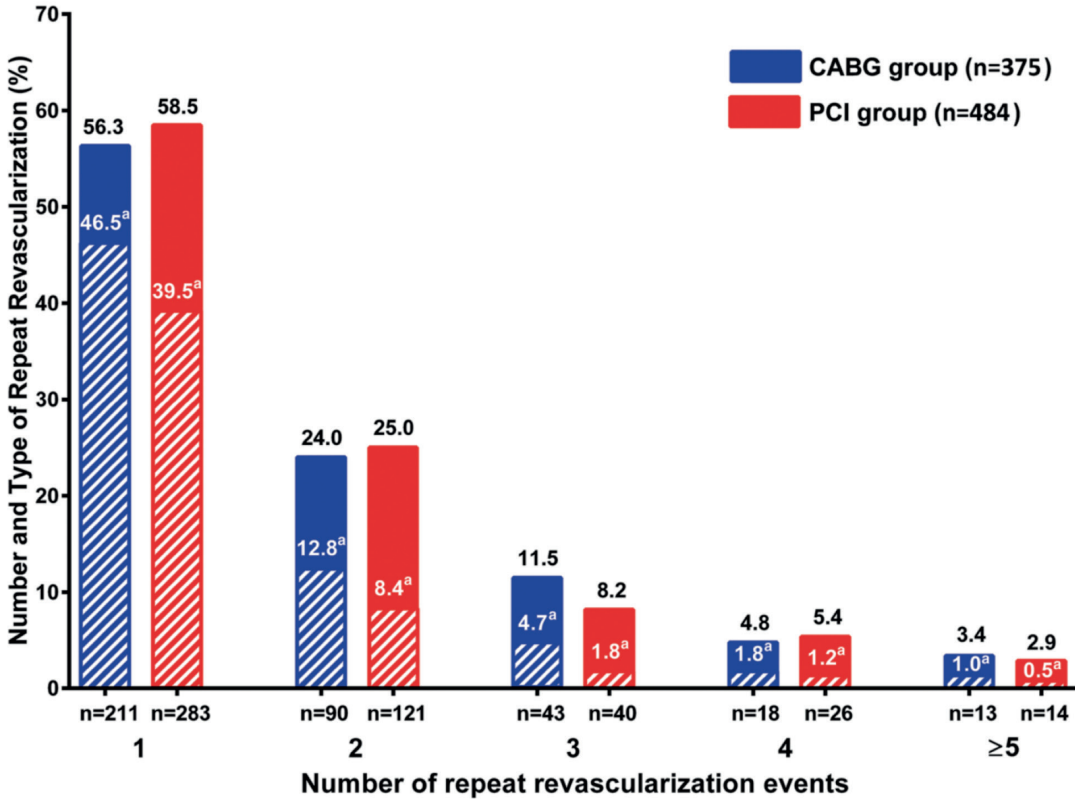


Figure 3. The proportion of patients undergoing the different numbers and types of repeat revascularization after CABG (blue) and PCI (red). Striped rectangles represent repeat CABG revascularization. *Percentage of CABG procedures. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

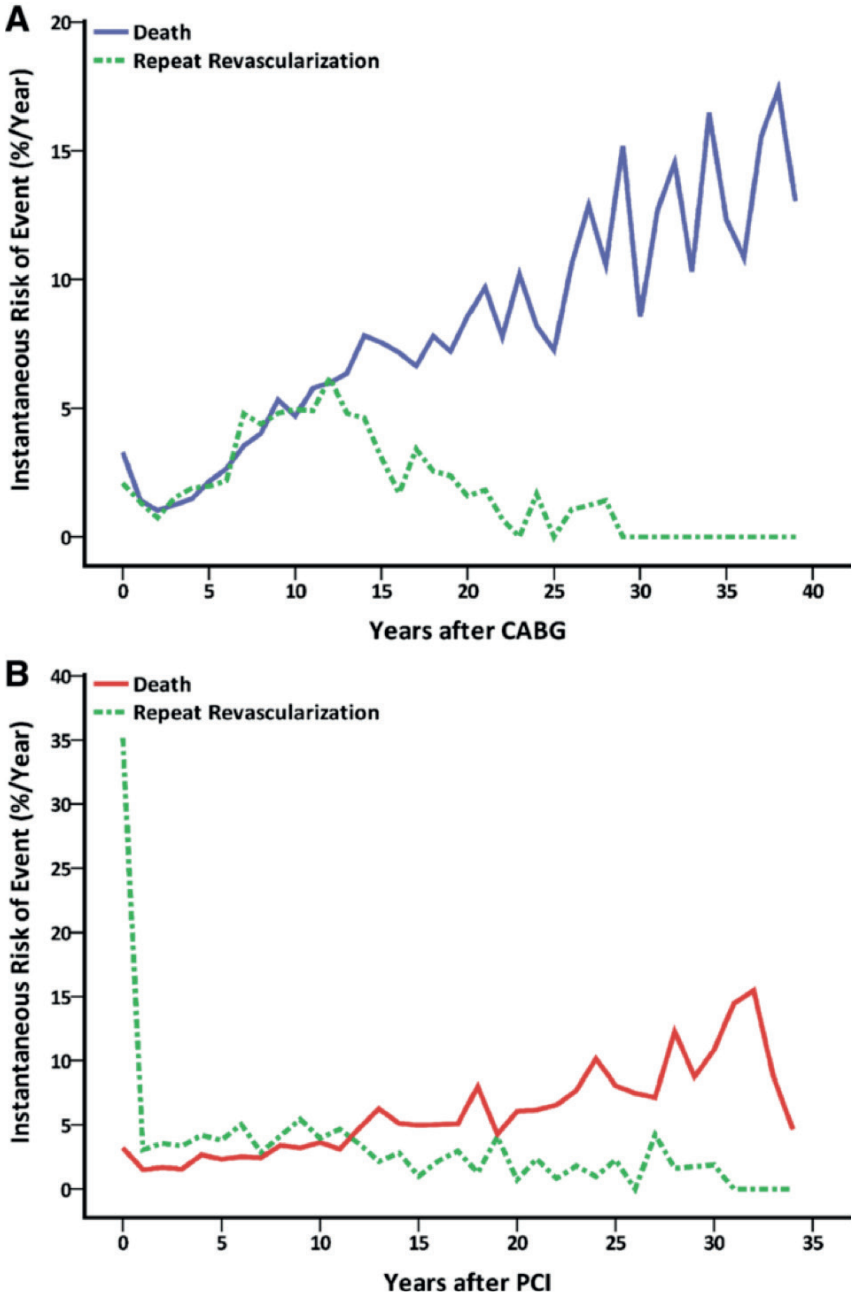


Figure 4. Instantaneous risk of death and repeat revascularization after CABG **(A)** and PCI **(B)**. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

DISCUSSION

To our knowledge, the presented data on life-long results after the first isolated venous CABG and PCI with balloon angioplasty procedures provide the longest, most unique and most complete follow-up information published to date. The main findings of this analysis can be summarized as follows: (i) Overall LE after venous CABG and PCI with balloon angioplasty was 18 and 17 years, respectively; (ii) the degree of complexity of the coronary disease had a significant impact on long-term survival, especially after PCI; (iii) in addition to the degree of coronary complexity, independent predictors of the 40-year survival rate were age, hypertension, diabetes, smoking and LV dysfunction; and (iv) rates of repeat revascularization were highest during the first year after PCI and during the 7-13 years follow-up period after CABG.

The coronary artery bypass grafting cohort

Advancements in the whole spectrum of patient care have led to significantly improved outcomes after CABG, which is still the standard of care in patients with advanced complex CAD (7, 8). Whereas other studies have reported 20 to 35 years of follow-up (9-11), this is the first study that provides life-long follow-up results after CABG surgery, with only 2% of the patients being lost to follow-up. Impressively, the 10-year survival rate is comparable to the findings from the more recent trials (12, 13). We found that venous CABG was associated with acceptable survival rates, probably for the following reasons: First, the majority (75%) of patients were under 58 years of age with preserved LV function and without significant comorbidities such as diabetes, thereby prolonging the lifespan of venous grafts. Secondly, considering that all patients were treated in the pre-PCI era, in situ stents did not complicate the surgical technique (14). Lastly, secondary prevention medications, modification of risk factors and repeat treatment interventions have changed notably during the follow-up period, which may have improved the life-expectancy.

The rate of repeat revascularization increased significantly 7 years after the initial CABG, most likely due to the loss of graft patency. However, these findings were derived before the widespread use of statins as secondary prevention, control of risk factors and modified surgical techniques that may have resulted in improved venous graft patency (15, 16). Furthermore, although the benefits of arterial grafts tend to increase with the duration of the follow-up (17), current European and American practice guidelines for arterial grafts are recommended for younger patients whose life expectancy is beyond the observed benefit of the vein graft (8, 18). This observation has motivated the design of the ongoing Arterial Revascularization Trial

(ART) study that compares the 10-year survival rates of patients with bilateral versus single internal mammary artery (IMA) grafting. The recent results of an interim analysis performed at 5 years follow-up show no significant differences between the 2 groups in the rates of major adverse events (19). However, considering our results, an increase in cardiac adverse events can be expected in the 5to 10-year follow-up period, which may result in the benefit of multiple arterial grafts at the 10-year as the ART study hypothesis. Nevertheless, the use of even the single IMA as the gold standard conduit for CABG produced surprisingly suboptimal results in recent studies (20), making the current results still clinically meaningful.

The percutaneous coronary intervention cohort

Treatment with PCI has evolved significantly over the last 40 years and has become a life-saving procedure in patients with acute indications (21) but also a treatment of choice for many patients with stable disease (8). Only a few studies have reported survival results longer than 10 years after PCI (22), whereas no very long-term follow-up data are available. In our study, only 3% of patients who had PCI were lost to follow-up, thereby providing an accurate estimate of long-term survival.

In 2012, Yamaji et al. reported a mortality rate of 59% at 20 years (22) compared to 53% in our study. However, the present study enrolled younger patients, only a few of whom had diabetes and a history of MI. In the Bypass Angioplasty Revascularization Investigation (BARI) clinical trial, the 10-year mortality rate was 55% in patients with diabetes compared to 23% in patients without diabetes (23). Patients with diabetes presenting for PCI are more likely to have more extensive CAD with accelerated atherosclerosis, thereby increasing the risk of MI, repeat revascularization and death (24). A recent pooled analysis of individual patient data from clinical trials shows that diabetes is one of the most critical determinants of the 5-year survival rate after PCI (25). We did not find diabetes to be a predictor of long-term death, probably because of the low number of patients who had diabetes. Additionally, the number of diseased vessels had a crucial impact on long-term survival after PCI. Similarly to results from previous trials using balloon angioplasty or bare-metal stents (26), the presence of 3-vessel disease was associated with a 3-fold increase in the mortality risk at 5 years compared to that of singleor 2-vessel disease. These data reflect the historical trends in PCI and may serve as a baseline for comparisons with the results of future PCI studies.

We found that the first PCI procedures with balloon angioplasty, in general, were associated with a high risk of repeat revascularization during the first year of follow-up. This risk was similar to rates reported from large randomized trials (27). However, it should be noted that the introduction of bare-metal stents and drug-eluting stents (DES) and the change from anticoagulation to antiplatelet therapies have markedly improved the efficacy of PCI by reducing acute coronary occlusion or the process of restenosis and hence the need for repeat revascularization (28). Furthermore, the results from the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial showed that the use of DES stents significantly decreased the necessity for repeat CABG procedures among patients randomized to the PCI group, although this was only assessed up to the 5-year follow-up (29). Nevertheless, the results from recent clinical trials comparing newer-generation DES with CABG have shown that the significant advantage of CABG over PCI concerning the incidence of repeat revascularization has remained, especially in patients with multivessel disease (30).

Study limitations

Our study has several significant limitations. Firstly, it is a cohort study of (s) elective patients from a tertiary referral centre that was designed 40 years ago. At that time, knowledge about the existence of risk factors was almost nonexistent. Therefore, only a limited number of baseline variables were collected. Secondly, surgical and percutaneous technology and techniques, periprocedural therapy and long-term guideline-directed secondary prevention medication have changed substantially since the time that the procedures in the current study were performed. Our findings therefore are not directly translatable to the current practice of CABG or PCI. In addition, no data were available on MIs and strokes occurring during the follow-up period.

CONCLUSIONS

Our findings demonstrate that CABG and PCI turned out to be excellent, durable treatments immediately after becoming a routine treatment, with a life expectancy of 18 and 17 years, respectively. Life-long follow-up studies such as these provide essential information for patients, clinicians and health care systems and may serve as landmark results for future life-long CABG and PCI reports.

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Chapter 4

Current Practice of State-of-the-Art Surgical Coronary Revascularization

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ABSTRACT

Coronary artery bypass grafting remains one of the most commonly performed major surgeries, with well-established symptomatic and prognostic benefits in patients with multivessel and left main coronary artery disease. This review summarizes current indications, contemporary practice, and outcomes of coronary artery bypass grafting. Despite an increasingly higher-risk profile of patients, outcomes have significantly improved over time, with significant reductions in operative mortality and perioperative complications. Fiveand 10-year survival rates are ≈85% to 95% and 75%, respectively. A number of technical advances could further improve shortand long-term outcomes after coronary artery bypass grafting. Developments in off-pump and no-touch procedures; epiaortic scanning; conduit selection, including bilateral internal mammary artery and radial artery use; intraoperative graft assessment; minimally invasive procedures, including robotic-assisted surgery; and hybrid coronary revascularization are discussed.

INTRODUCTION

Coronary artery disease is one of the leading causes of death in Western countries. Since the introduction of coronary artery bypass grafting (CABG) in the 1960s (1), it has rapidly become one of the most commonly performed major surgical procedures (2). Outcomes have significantly improved over time, with declining rates of operative mortality and major morbidity, which may be due in part to better patient selection, improved surgical techniques, and better alternative techniques in patients presenting with cardiogenic shock (eg, mechanical support devices) (3). Large multicenter randomized and observational studies have reported excellent short-term outcomes (4,5).

Despite the rise in rates of percutaneous coronary intervention (PCI) and the technical advances in stent design, CABG remains crucial for patients with multivessel coronary disease that is too complex to be treated optimally with PCI (6-8). According to data from the Organisation for Economic Cooperation and Development, CABG is on average performed at a rate of 44 per 100 000 individuals (Figure 1) (9).

In this review, we discuss contemporary indications for CABG, practice patterns, and outcomes. We also discuss specific surgical techniques and a number of technical advances that have received attention over the last decade and could potentially improve shortand long-term outcomes after CABG.

CONTEMPORARY INDICATIONS, PRACTICE, AND OUTCOMES

Preoperative Risk Assessment

The choice of percutaneous or surgical revascularization depends on the risk-tobenefit ratio of procedures and should be decided by a multidisciplinary heart team that includes at least an interventional cardiologist and cardiovascular surgeon but can be expanded according to the status of the patient with an anesthesiologist, nephrologist, geriatrist, etc. (10). To determine which treatment strategy should be favored and what the risks of surgical intervention are, preoperative risk assessment is crucial. Several risk scores have been established to estimate the surgical predicted risk of mortality. The most widely used scores are the EuroSCORE (II) and the Society of Thoracic Surgeons' risk model, with the latter also providing a calculated risk of stroke, renal failure, sternal wound infection, and length of stay (11,12). Although these models include different variables, risk factors can be categorized as follows: (1) demographic variables such

as age and sex; (2) previous cardiovascular events, including prior cardiovascular surgery or intervention, myocardial infarction, and stroke or transient ischemic attack; (3) cardiovascular variables, which include left ventricular function, diabetes mellitus, hypertension, arrhythmias, and peripheral vascular disease; (4) noncardiovascular variables, including renal failure and chronic obstructive pulmonary disease; (5) disease complexity and pathology, that is, the number of diseased vessels, degree of valve stenosis and regurgitation, and presence of endocarditis; and (6) the hemodynamic status of the patient and the urgency of surgery. In studies comparing the Society of Thoracic Surgeons' score and EuroSCORE II models in patients undergoing isolated CABG, the Society of Thoracic Surgeons' score and EuroSCORE II performed similarly (13,14).However, despite the comprehensiveness of these models, additional comorbid factors such as pulmonary hypertension, liver disease, previous chest radiation, and the frailty status of the patient are not included in either model but increase surgical risk and may play an important role (15). The degree and complexity of coronary disease do not appear to affect shortor long-term outcomes after CABG, as shown in the SYNTAX trial (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery). The SYNTAX score quantifies the complexity of coronary artery disease by the location and length of lesions, presence of a chronic total occlusion, bifurcation or trifurcation lesions, severe lesion calcification, vessel tortuosity, and diffuse disease and small vessels, and it has been proved to be a predictor of prognosis after PCI but not CABG. It is therefore a robust factor to differentiate which patients are candidates for CABG rather than PCI and is recommended for use in both the US and European clinical guidelines (16,17). In patients in whom the risk-to-benefit ratios of percutaneous and surgical revascularization are similar, the patients' preferences should strongly influence the treatment strategy.

The appropriate diagnostic workup of patients before revascularization should thus include a full medical history, an ECG, laboratory assessments, cardiac echocardiography, and coronary angiography. Although notuniversally performed, preoperative carotid ultrasound should be routinely considered to detect carotid lesions that are linked to stroke.

Procedural Characteristics of Contemporary CABG

The majority of CABG procedures are performed through a median sternotomy with the use of cardiopulmonary bypass so that the heart can be arrested, thereby producing ideal conditions to allow a technically less demanding procedure. During on-pump surgery, the heart is arrested with cardioplegia, a potassium-

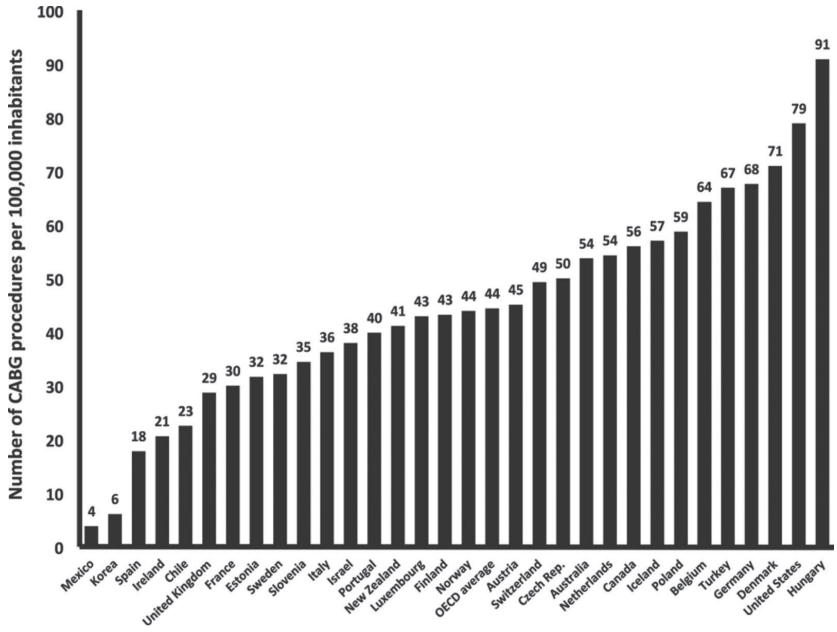


Figure 1. Number of coronary artery bypass graft (CABG) operations per 100 000 inhabitants. All data are from 2013 except for data from Hungary (2012), Belgium (2012), Australia (2012), Canada (2012), Turkey (2012), Chile (2012), the Netherlands (2010), the United States (2010), Iceland (2009), Portugal (2009), and Switzerland (2008). Data are from the Organisation for Economic Cooperation and Development (OECD) (9).

rich solution to inhibit the depolarization/repolarization cycle of myocardial cells, for myocardial preservation. Ischemic preconditioning may further reduce myocardial ischemia but has not been shown to reduce clinical outcomes (18).

Off-pump coronary artery bypass (OPCAB) procedures, however, do not require cardiopulmonary bypass and cardioplegia because the heart continues to beat. It is a technically more demanding procedure but theoretically reduces complications of cardiopulmonary bypass related to a systemic inflammatory reaction syndrome, microemboli, an increased blood-brain barrier permeability, and aortic manipulation for cross-clamping and cannulation to the heart-lung machine. An overview of CABG procedures performed in the United States showed that the percentage of procedures performed off-pump peaked at 23% in 2002 but declined to 17% in 2012 (19).

The choice of conduits to bypass coronary lesions has been a continuous debate since the use of a single internal mammary artery (IMA) graft proved to have superior long-term outcomes over saphenous vein grafts. However, despite 3 guidelines with recommendations for increasing the use of arterial conduits, including 1 dedicated guideline from the Society of Thoracic Surgery in 2016 on conduit selection for CABG (Table 1), rates of multiple arterial grafting with IMA grafts and/ or the radial artery remain persistently low. In the United States between 2002 and 2005, the rate of bilateral IMA (BIMA) use was only 4% (21). In contemporary practice, the vast majority of CABG procedures are performed with the left IMA (LIMA) anastomosed to the left anterior descending artery (LAD) and additional stenoses bypassed with vein grafts to perform complete revascularization. However, there is significant variability in how CABG procedures are performed in different countries in terms of the use of cardiopulmonary bypass, the type of cardioplegia, and which conduits are used (22).

Short-Term Complications and Long-Term Prognosis

Complication rates of CABG are typically measured at 30 days and include death, stroke, myocardial infarction, re-exploration for bleeding, renal failure requiring dialysis, atrial fibrillation, and deep sternal wound infection (eg, mediastinitis; Table 2). In most reports of large series of isolated CABG, early mortality rates are 1% to 2%, and higher mortality is reported for patients at higher risk in emergent scenarios or because of multiple comorbidities and advanced age. Although outcomes have improved, CABG still carries a considerable risk of morbidity.1 Neurological complications include stroke in 1% to 3% and delirium in 8% to 50% of patients. The rate of myocardial infarction differs significantly among studies because of varying definitions, including changes on the ECG or cardiac enzyme elevations, but is estimated to occur at a rate of 2% to 4%. About 3% of patients with myocardial infarction have clinical hemodynamic instability resulting from early graft failure; the majority of patients will be managed by PCI, although some patients will require surgical reoperation. Reoperation is required in 2% to 4% of patients because of bleeding complications and increases the risk of other complications; bleeding can be reduced by blood conservation techniques, including cell-saver machines, antifibrinolytics use, and platelet and plasma transfusions. Some degree of renal failure is frequent after CABG, but only about 1% of patients require dialysis. About 15% to 30% of patients have new-onset atrial fibrillation that is usually transient. Mediastinitis develops in 0.5% to 3% of patients and causes long lengths of stay and recovery time and frequently requires sternal debridement or reconstruction. Although concerns about neurocognitive

decline after CABG resulting from cardiopulmonary bypass have been raised (23), large randomized studies have found preserved neurocognitive function after both on-pump or off-pump surgery (24).

Length of stay after isolated CABG and combined CABG and valve procedures is ≈7 and 10 days, respectively (25). Patients are limited in their activities during the first 6 weeks after CABG because of the general effects of major surgery and anesthesia and the sternotomy, which requires time to heal. After discharge, cardiac rehabilitation optimizes physical, psychological, and social functioning of patients after CABG to increase quality of life (26). Clearly, lifestyle changes, including smoking cessation, healthy food choices, and exercising, improve long-term prognosis. Moreover, educa-tion on long-term secondary prevention compliance is essential. Compliance rates of taking antiplatelet medications, β-blockers, statins, and angiotensin-converting enzyme inhibitors after CABG are suboptimal, even though optimal medical therapy significantly improves long-term outcomes (27). Intense or maximally tolerated statin therapy should be prescribed to reach a low-density lipoprotein cholesterol target <70 mg/dL. β-Blockers should be initiated in patients with a preoperative myocardial infarction or reduced left ventricular ejection fraction (<35%). In addition, angiotensin-converting enzyme inhibitors should be given to patients with reduced left ventricular function (<40%) and a glomerular filtration rate >30 ml/min per 1.73 meter squared. There is currently no consensus on the routine use of dual antiplatelet therapy after CABG.

Results of major adverse cardiac or cerebrovascular events at 5-year follow-up from large, contemporary CABG trials show that all-cause mortality at 5 years ranges between 5% and 15%, myocardial infarction between 2% and 8%, and stroke between 1% and 4%, depending on the population and definitions used (Table 3). Repeat revascularization ranges between 2% and 15% and depends on whether it is performed for anatomic or ischemic reasons. Historically, survival at 10 years is ≈75% (35,36) but may prove to be higher in contemporary practice, especially with higher use of guideline-directed medical therapy.

Table 1. Guideline Recommendations for Conduit Use During Coronary Artery Bypass Grafting.

	2011 ACCF/AHA (17)	2016 STS (20)	2014 ESC/EACTS (16)
LAD territory	"If possible, the LIMA should be used to bypass the LAD artery if indicated" (Class I, Level of Evidence B) "The RIMA is probably indicated to bypass the LAD artery when the LIMA is unavailable or unsuitable as a bypass conduit" (Class IIa, Level of Evidence C)	"The IMA should be used to bypass the LAD artery when bypass of the LAD is indicated" (Class I, Level of Evidence B)	"Arterial grafting with IMA to the LAD system is recommended" (Class I, Level of Evidence A)
BITA	"When anatomically and clinically suitable, use of a second IMA to graft the left circumflex or right coronary artery (when critically stenosed and perfusing LV myocardium) is reasonable to improve the likelihood of survival and to decrease reintervention" (Class IIa, Level of Evidence B)	"Use of BIMAs should be considered in patients who do not have an excessive risk of sternal complications" (Class IIa, Level of Evidence B)	"BIMA grafting should be considered in patients < 70 yr of age" (Class IIa, Level of Evidence B)
RA	"Use of a RA graft may be reasonable when grafting left-sided coronary arteries with severe stenosis (>70%) and right-sided arteries with critical stenosis (≥90%) that perfuse LV myocardium" (Class IIb, Level of Evidence B)	"As an adjunct to LIMA to LAD (or in patients with inadequate LIMA grafts), use of a RA graft is reasonable when grafting coronary targets with severe stenosis" (Class IIa, Level of Evidence B)	"Use of the RA is recommended only for target vessels with high-degree stenosis" (Class I, Level of Evidence B)
Gastroepiploic artery	No recommendation provided	"The RGEA may be considered in patients with poor conduit options or as an adjunct to more complete arterial revascularization" (Class IIb, Level of Evidence B)	No recommendation provided
Total arterial revascularization	"Complete arterial revascularization may be reasonable in patients less than or equal to 60 yr of age with few or no comorbidities" (Class IIb, Level of Evidence C) "Arterial grafting of the right coronary artery may be reasonable when a critical (≥90%) stenosis is present" (Class IIb, Level of Evidence B)	"As an adjunct to LIMA, a second arterial graft (RIMA or RA) should be considered in appropriate patients" (Class IIa, Level of Evidence B)	"Total arterial revascularization is recommended in patients with poor vein quality independently of age" (Class I, Level of Evidence C) "Total arterial revascularization should be considered in patients with reasonable life expectancy" (Class IIa, Level of Evidence B)

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; BIMA, bilateral internal mammary artery; BITA, bilateral internal thoracic artery; EACTS, European Association for CardioThoracic Surgeons; ESC, European Society of Cardiology; IMA, internal mammary artery; LAD, left anterior descending; LIMA, left internal mammary artery; LV, left ventricular; RA, radial artery; RGEA, right gastroepiploic artery; RIMA, right internal mammary artery; and STS, Society of Thoracic Surgeons.

Indications for CABG

CABG is indicated for both relief of symptoms and prolongation of life. Patients with stable coronary artery disease in whom medical therapy fails to significantly reduce symptoms are generally evaluated for myocardial revascularization. Evidence from the latest randomized trials showed that CABG appeared particularly beneficial for patients with more severe and complex coronary artery disease. Subgroup analyses from the SYNTAX trial showed that the difference between CABG and PCI treatment was evident only in those with intermediate or high severity of disease as determined by the SYNTAX score (37,38). Diabetic patients often have diffusely diseased vessels with progressive atherosclerosis. CABG provides a improved long-term prognosis particularly in these patients (7). Indeed, clinical guidelines recommend that CABG be performed in patients with complex disease, as well as in diabetic patients (16,17). With continuous improvements in both CABG and PCI technology, recommendations for which revascularization strategy should be preferred for a specific patient continue to evolve on the basis of new results from randomized trials and vary significantly between different geographical regions.

Whether CABG should be performed in patients with ischemic cardiomyopathy has recently been investigated in the STICH trial (Surgical Treatment for Ischemic Heart Failure). Among 1212 patients with a left ventricular ejection fraction <35% who were randomly assigned to CABG or medical therapy, 10-year outcomes favored CABG over medical therapy for all-cause death (58.9% versus 66.1%, respectively; P=0.02) and cardiovascular death (40.5% versus 49.3%, respectively; P=0.006) (39). The impact of CABG on cardiovascular death remained consistent over all ages (40). From these results, an evidence basis for the indication of CABG in patients with poor ejection fraction is substantiated.

Table 2. Incidence, Predictors, and Reductions of Short-Term Complications After Coronary Artery Bypass Grafting.

Complication	Incidence, %	Important Specific Predictors	How to Potentially Reduce Its Occurrence
Mortality	1–2	Cardiovascular risk factors Comorbidities: renal failure, lung disease, neurological impairment, etc Patient status Urgency of procedure	Reduce procedural invasiveness Adequate patient selection in multidisciplinary heart team meetings Delaying CABG in patients with an acute myocardial infarction whenever possible Increasing the use of mechanical support devices in patients with cardiogenic shock
Stroke	1–3	Previous stroke or transient ischemic attack Peripheral vascular disease, including carotid disease Preoperative and postoperative de novo atrial fibrillation Hypertension Severe atherosclerotic aorta	Off-pump CABG Clampless/no-touch procedures Epiaortic scanning
Myocardial infarction	2–4	Recent myocardial infarction Urgency of procedure Procedural factors, including the graft configuration, number of distal anastomoses, incomplete revascularization, and longer cardiopulmonary bypass time Procedural problems related to insufficient myocardial protection, air embolism, and anastomoses	Sufficient myocardial protection with cardioplegia and thermal regulation Operative graft flow measurement using TTFM
Re-exploration for bleeding	2–4	Body surface area or body mass index Immunosuppressive therapy Preoperative antiplatelet or anticoagulation use Prior cardiovascular surgery Urgency of procedure Complexity of coronary disease or number of distal anastomoses	Preoperative timely discontinuation of antiplatelet or anticoagulation therapy Delaying surgery until the effect of antiplatelets has worn off Platelet function testing for optimal timing of surgery Perioperative antifibrinolytic agents, platelets, and fresh-frozen plasma
Delirium	8–50	Older age Cognitive function Prior cerebrovascular disease Duration of cardiopulmonary bypass	Preoperative screening Avoid postoperative infection Multicomponent intervention to manage cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration
Renal failure requiring dialysis	1	Preoperative renal function Diabetes mellitus Preoperative status (eg, cardiogenic shock)	Off-pump CABG
Atrial fibrillation	15–30	Peripheral vascular disease Preoperative atrial fibrillation Obesity	Medication such as amiodarone or sotalol, antiinflammatory corticosteroids, β-blockers, statins, antioxidant agents such as N-acetylcysteine, ACE inhibitors, and omega-3 fatty acids
Mediastinitis	0.5–3	Obesity Diabetes mellitus Hypertension Preoperative renal failure on dialysis Prior cardiovascular surgery Duration of cardiopulmonary bypass Bilateral IMA use Re-exploration for bleeding	Preoperative hygiene including preoperative antiseptic showers and hair removal Perioperative antibiotics Specific patient selection for bilateral IMA use Vancomycin paste Optimal glycemic control

ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass grafting; IMA, internal mammary artery; and TTFM, transit-time flow measurement. Modified from Head et al[1] with permission of the publisher.
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Table 3. Five-Year Outcomes After Contemporary Coronary Artery Bypass Grafting.

				5-Year Outcomes of CABG, %					
Trial	Patient Inclusion	Trial Setup	Inclusion and Patients, n	Death	MI	Stroke	Death+ Stroke+MI	Repeat Revascularization	MACCEs
SYNTAX trial[6]	Multivessel or left main disease	PCI vs CABG	2005–2007 n=1800	11.4	3.8	3.7	16.7	13.7	26.9
MASS III trial[28]	Multivessel disease	Onvs off-pump	2001–2006 n=308	5.2–8.4	1.9–6.5	1.9–3.2	…	5.9–6.5	…
FREEDOM trial[7]	Multivessel disease, diabetics	PCI vs CABG	2005–2010 n=1900	10.9	6.0	5.2	…	…	…
PRECOMBAT trial[29]	Left main disease	PCI vs CABG	2004–2009 n=600	7.9	1.7	0.7	9.6	5.5 (Ischemia driven)	14.3
PREVENT IV trial[30]	All coronary artery disease	Prevention of graft failure with edifoligide	2002–2003 n=3014	10.9–12.5	…	…	…	…	…
BEST trial[31]	Multivessel disease	PCI vs CABG	2008–2013 n=880	5.0	2.7	2.9	9.5	5.4	13.3
NOBLE trial[32]	Left main disease	PCI vs CABG	2008–2015 n=1201	9	2 (Nonprocedural)	2	…	10	19
CORONARY trial[33]	All coronary artery disease	Onvs off-pump	2006–2011 n=4752	13.5–14.6	7.5–8.2	2.3–2.8	…	2.3–2.8	…
ART Trial[34]	Multivessel disease	Single vs double IMA use	2004–2007 n=3102	8.4–8.7	3.4–3.5	2.5–3.2	12.2–12.7	6.5–6.6	

ART indicates Arterial Revascularization Trial; BEST, Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; CABG, coronary artery bypass grafting; CORONARY, Coronary Artery Bypass Surgery (CABG) Off or On Pump Revascularization Study; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; IMA, internal mammary artery; MACCE, major adverse cardiac or cerebrovascular event; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; PREVENT IV, Project of Ex-Vivo Vein Graft Engineering via Transfection IV; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.

When patients are evaluated for revascularization, results from a coronary angiogram provide necessary information on which vessels require revascularization. Because visual inspection of coronary angiograms can be subjective and cannot always estimate the functional significance of a lesion to flow, fractional flow reserve (FFR) is frequently used to quantify the degree of stenosis in terms of a pressure drop across a coronary lesion. An FFR ≤0.80 is generally considered to be a significant stenosis (41). Although FFR-guided revascularization has been shown to be associated with significantly improved outcomes after PCI (42), evidence from studies evaluating FFRguided CABG is scarce. Toth and coauthors (43) compared angiographyand FFR-guided CABG and reported that FFR-guided CABG was associated with fewer anastomoses and a higher rate of off-pump procedures but with comparable rates of the composite of death, myocardial infarction, and target vessel revascularization at 3-year follow-up in the largest study to date.

CONDUITS

BIMA Use

A large body of clinical and angiographic evidence supports the use of BIMA instead of a single IMA graft with additional venous conduits. Particularly in younger patients, the benefit of BIMA use is apparent, with the age cutoff estimated at 60 to 70 years (44,45). This may be the result of the combination of a longer life expectancy of younger patients and diverging survival curves between single IMA and BIMA use with longer follow-up. A meta-analysis of studies with a follow-up duration of >9 years found that among 15 583 patients enrolled in 9 observational studies, survival was significantly improved in patients in whom BIMA grafts were used as opposed to a single IMA graft, with a hazard ratio (HR) of 0.79 (95% confidence interval (CI), 0.75–0.84) (46). However, some surgeons may be reluctant to perform BIMA grafting because of fear of an increased risk of deep sternal wound infections; this risk is most apparent in female patients with obesity, diabetes mellitus (particularly those with poorly regulated diabetes mellitus), renal failure, and chronic obstructive pulmonary disease. To limit the risk of sternal wound infections, skeletonized rather than pedicled harvesting of IMA grafts is preferred because it maintains sternal vasculature, which significantly reduced the risk of sternal wound complications in a recent analysis (47).

ART (Arterial Revascularization Trial) randomly assigned 3102 patients to BIMA or single IMA use and is likely to provide a definitive answer on whether BIMA should be performed more routinely. Short-term safety rates were comparable for groups with single IMA and BIMA use, with 30-day mortality rates of 1.2% in both groups and comparable rates of stroke, myocardial infarction, and repeat revascularization, although there was an increased risk for sternal reconstruction with BIMA use (5). Recent completion of a 5-year midterm follow-up showed that there was no difference between BIMA and single IMA use for the primary end point of death (8.7% versus 8.4%, respectively; P=0.77) or in terms of mortality, myocardial infarction, and stroke (12.2% versus 12.7%, respectively; P=0.69) (34). This may be the result of the use of a radial graft in 20% of patients in the single IMA group, which could have improved outcomes in that group by providing a second arterial conduit. Moreover, rates of adherence to optimal medical therapy for secondary prevention were excellent in both groups, perhaps limiting early vein graft failure. The study was not powered to detect a difference at 5-year follow-up and will continue to 10 years. Indeed, the benefit of BIMA is often seen with increased follow-up because vein graft failure accelerates after 5 years.

When CABG with BIMAs is performed, whether to use both arteries in situ or in a Y or T configuration remains a matter of debate. A recent randomized controlled trial of 304 randomized patients concluded that the primary end point of graft patency at 3-year follow-up was comparable for composite grafting and in situ grafts, and there were no differences in the rates of all-cause survival and myocardial infarction (48). However, composite grafting significantly reduced the rate of repeat revascularization over 7-year follow-up, probably because of more complete arterial revascularization with composite grafts: 3.2±0.8 distal anastomoses were placed versus 2.4±0.5 with in situ grafts (P<0.01).

Radial Artery Use

The radial artery is often used in patients in whom BIMA use is not feasible or advised or to augment the number of arterial grafts performed in addition to BIMA grafting to accomplish total arterial revascularization. Numerous randomized controlled trials have compared graft patency of radial arteries and vein grafts. A metaanalysis of 5 trials found that radial artery grafts were associated with significantly better graft patency than vein grafts (49) but without reductions in all-cause death in underpowered analyses (50,51). Several propensitymatched observational studies showed that the radial artery improved long-term survival over the use of vein grafts (52,53). The radial artery has furthermore been compared with the right IMA (RIMA) in addition to a LIMA to the LAD. In the

RAPCO trial (Radial Artery Patency and Clinical Outcomes), a total of 394 patients <70 years of age were assigned to receiving a radial artery or free RIMA; at a mean follow-up of 5.5 years, the Kaplan-Meier estimates of graft patency were 89.8% and 83.2%, respectively (*P*=0.06), although 10-year follow-up is awaited (54). A meta-analysis of 8 propensitymatched analyses including 15374 patients reported a significantly better survival with a RIMA graft than with a radial artery, with a HR of 0.75 (95% CI, 0.58–0.97; P=0.03) (55). Therefore, it has been proposed that the radial artery be used as an alternative to the RIMA in patients with a high risk of mediastinitis or to graft the highly stenosed right coronary artery or distal circumflex territory.

Recent interest has been directed to determining whether the radial artery as an adjunct to BIMA use is superior to additional vein grafts. Benedetto and colleagues (56) reported that survival of 275 propensitymatched pairs, after a mean follow-up of 10.6 years, was comparable between patients receiving a radial artery and those receiving a vein graft in addition to BIMA use (*P*=0.54). Grau and colleagues (57), however, reported that, although 15-year survival was comparable between BIMA with radial or vein grafting, survival beyond the 10-year follow-up appeared to be significantly better with a radial artery. Impressively, Shi and colleagues (58) reported that 15-year survival was 82% versus 72% in patients receiving a radial versus vein graft as a third conduit (*P*=0.021) in an analysis of 262 propensity-matched pairs.

If a radial artery is used, it should be anastomosed only to coronaries with a high-grade stenosis (>90%) to avoid competitive flow that may otherwise lead to a "string sign" of the conduit. In the RAPS trial (Radial Artery Patency Study; n=440), the rate of graft occlusion was 11.8% in patients with 70% to 89% stenosis in the native vessel but only 5.9% in patients with ≥90% stenosis (*P*=0.03) (59).

Saphenous Vein Graft Optimization

In current practice, almost 80% of all bypass conduits are saphenous veins because of their ease of harvesting and the lesser technical challenge of vein grafting compared with multiple arterial grafting. Although recent studies have shown excellent outcomes with vein grafts compared with the RIMA as part of a Y configuration with LIMA inflow (60), the major disadvantage of the saphenous vein is its tendency for progressive failure during follow-up (61). Despite the higher use of optimal medication in recent studies, particularly antiplatelet therapy and statins, saphenous vein grafts still show a significant failure rate (62). However, vein graft patency could be improved. First, Samano and colleagues (63) have

now reported a 16-year follow-up of a no-touch technique for vein graft harvest that resulted in significantly better patency than conventional skeletonized vein harvesting, which may be the result of reduced intimal hyperplasia and protection against distension-induced damage that preserves vessel morphology and nitric oxide secreting activity (64). The use of endoscopic vein harvesting to reduce the rate of wound infections, wound dehiscence, and overall complications compared with open vein harvesting raised concerns about reduced graft patency because of the potential for increased damage to the conduit with endoscopic techniques. However, 2 large observational studies reported no long-term excess of all-cause mortality or myocardial infarction with endoscopic vein harvesting compared with open vein harvesting (65,66). Second, exploratory work from the PREVENT IV trial (Project of Ex-Vivo Vein Graft Engineering via Transfection) reported that storage of vein grafts in a buffered solution provided significantly improved graft patency and tended to reduce the rate of adverse clinical outcomes at 5 years compared with vein grafts stored in normal saline or blood (67). Although many solutions have been developed, large-scale studies are not yet available. Third, both Taggart and colleagues (68) and Meirson and colleagues (69) have reported that the use of an external stent for saphenous vein grafts significantly reduced intimal hyperplasia at the 1-year follow-up, perhaps as a consequence of a lower oscillatory shear index that results in less turbulent flow. Larger studies with longer follow-up are required to determine whether this translates into improved vein graft patency and ultimately improved clinical outcomes.

Intraoperative Graft Assessment

CABG is the only major vascular surgical procedure that is not routinely assessed with a “completion angiogram” or other imaging study at the time of surgery. In all other vascular surgical procedures, this intraoperative quality assessment is considered routine and necessary. Although intraoperative angiography remains impractical on a routine basis for CABG except in a hybrid operating room, some quantitative and qualitative assessment of graft flow and function may be considered in CABG.

Suboptimal rates of graft patency may be potentially related to operative technical issues such as anastomotic imprecision, graft kinking, and limited graft outflow. Therefore, several methods have been introduced as intraoperative graft assessment tools to check for technical issues that could be resolved during the operation. Transit-time flow measurement (TTFM) is the most widely used technique because of its user-friendliness and comprehensive validation. Among studies that applied TTFM during CABG, 2% to 4% of grafts required

revision (70,71). Studies that have related TTFM findings to shortand longer-term outcomes have been controversial, although the majority of studies found that either graft flow or pulsatility index was a predictor of short-term complications, as well as death and graft failure during follow-up (71). Although TTFM is valuable to identify truly poor and truly good grafts, its value is limited in identifying grafts with minor abnormalities that may present false-negative values of pulsatility index and flow. As a result, recent studies have suggested that 2 parameters, graft flow and anastomotic patency, are required for the complete assessment of bypass grafts. TTFM combined with epicardial echocardiography is an approach that provides both a functional and an anatomic assessment of bypass grafts. In a recent article by Di Giammarco and coauthors (72), the positive predictive value of TTFM was increased from 10% to almost 100% if epicardial echocardiography was also performed to directly image flow through the graftcoronary anastomosis.

OFF-PUMP AND AORTIC MANIPULATION

Off-Pump Surgery

More than 60 randomized trials have compared offpump with on-pump CABG. Several meta-analyses of these trials performed at different time points and with different inclusion criteria all come to a uniform conclusion: OPCAB significantly reduced short-term rates of stroke and renal failure but did not reduce the risk of mortality or myocardial infarction in lowand mixedrisk patients (73,74). Specific studies in high-risk patients found a significant reduction in mortality with OPCAB compared with on-pump CABG in high-risk patients, although at the price of higher rates of repeat revascularization (74,75).

Two of the largest contemporary trials (CORONARY trial (CABG Off or On Pump Revascularization Study), n=4752, and GOPCABE trial (German Off Pump Coronary Artery Bypass in Elderly Study), n=2539) noted that there were comparable 1-year rates of mortality, stroke, myocardial infarction, renal failure requiring dialysis, and repeat revascularization, as well as composite end points of these events (76). The CORONARY trial recently reported results at the 5-year follow-up; there were still no differences in any of the clinical end points, with identical survival between the 2 techniques at 5 years (33). Concerns about OPCAB procedures are particularly related to the potential for a lower rate of complete revascularization and compromised graft patency. Whether there is an impact of onor off pump surgery on survival remains highly controversial. In a recent single-center analysis of 13 226 patients, 10-year risk-adjusted survival was nearly

identical between onand off-pump CABG (72.8% versus 72.1%, respectively; *P*=0.56), as was the freedom from death and reintervention (*P*=0.23) (77). Routine intraoperative TTFM may be of particular value to the OPCAB surgeon to ensure optimal graft patency during challenging cases.

One of the fundamental issues with OPCAB remains the experience and expertise of the surgeon. The multi-center ROOBY trial (Randomized On/Off Bypass) reported significantly better outcomes with on-pump CABG but was severely criticized because of strikingly asymmetrical experience with on-pump versus off-pump CABG among the enrolling surgeons (78). In trials that required substantial experience of participating surgeons such as CORONARY and GOPCABE, outcomes of OPCAB have not been inferior (33,76). A recent study found that OPCAB outcomes were best if a surgeon performed >50 OPCAB procedures annually (79), although another study suggested that outcomes were not dependent on the level of the operator being a trainee or attending (80). It has become clear that the experience of not only a specific surgeon but also the entire hospital matters in optimizing outcomes with OPCAB (81). For this reason, clinical guidelines recommend that OPCAB be performed in high-volume off-pump centers (16).

Clampless and No-Touch Surgery

One particular potential benefit of OPCAB procedures is the possibility of avoiding manipulation of the aorta. However, OPCAB has most commonly been performed with the use of a side clamp for proximal anastomoses, which increases the risk of hard and soft plaque emboli that could cause neurological events. Some critique has been directed to studies comparing OPCAB and onpump CABG for not specifically avoiding any manipulation of the aorta by using either proximal anastomosis devices or a conduit configuration that still requires a proximal anastomosis. This may explain why perioperative stroke reduction with OPCAB has not been more impressive. A propensity-matched analysis reported a trend toward a significant reduction in in-hospital allcause mortality associated with avoiding aortic clamping in addition to a significantly lower rate of stroke (82). Indeed, aortic manipulation has been found to be associated with postoperative major adverse events, and any reduction of aortic manipulation, by clamping only once instead of multiple times, reduces the risk of stroke. Therefore, the weight of evidence suggests that the surgical approach associated with the lowest risk of perioperative stroke appears to be a no-touch, total arterial off-pump CABG (Figure 2); a network metaanalysis of 13 studies and 37720 patients supports this recommendation by showing significant reductions mortality, stroke, and renal failure when this technique is applied (83). Even if on-pump surgery

is performed and the aorta is cross-clamped, stroke rates can be reduced by not performing multiple clamping or avoiding sidebiting clamp techniques.

Epiaortic Scanning

Surgeons generally palpate the aorta before cannulating or constructing a proximal anastomosis to detect in atherosclerotic burden that is present in >50% of patients who undergo CABG. However, aortic palpation has limited sensitivity because of the inability to palpate the complete circumference of the aorta and to detect soft plaques. Consequently, epiaortic ultrasonography has been recommended to detect plaque, and several large retrospective studies of all cardiac surgery operations and specifically CABG procedures found that the use of epiaortic ultrasound significantly reduced the incidence of stroke (84,85). This reduction in stroke is achieved by modifying the surgical technique when significant plaque is detected. The need for technique modifications based on epiaortic ultrasonography ranges between 4% and 31% (85,86), depending on the type of modification and the definitions used. On the basis of these findings, intraoperative epiaortic scanning should be considered before aortic manipulation.

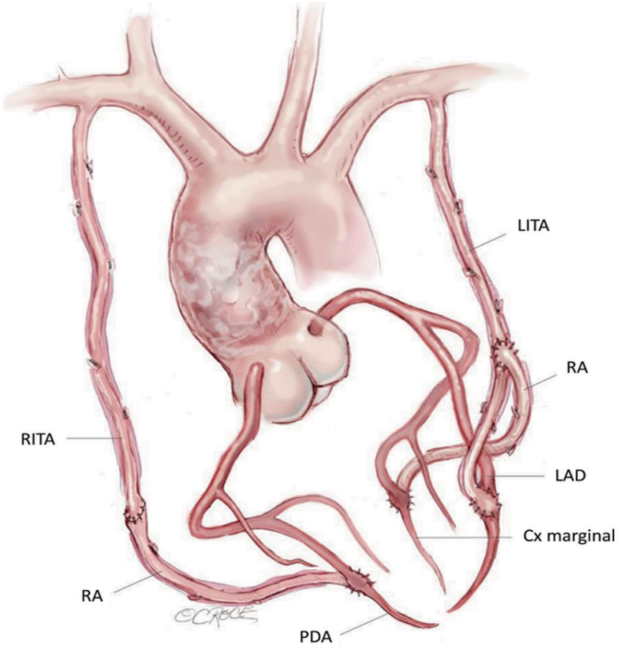


Figure 2. Example of a complete arterial no-touch coronary artery bypass graft configuration
Cx indicates circumflex; LAD, left anterior descending; LITA, left internal thoracic artery; PDA, posterior descending artery; RA, radial artery; and RITA, right internal thoracic artery.

REDUCING INVASIVENESS

Minimally Invasive CABG

An alternative approach to a sternotomy for CABG may be to perform minimally invasive direct coronary artery bypass (MIDCAB) via a small (5–10 cm) left anterior thoracotomy. The LIMA can then be harvested by direct vision or with robotic endoscopic techniques. The largest series by Holzhey and colleagues (87) of 1768 patients undergoing MIDCAB from 1996 to 2009 reported a postoperative mortality of 0.8% and a 95.5% graft patency at routine postoperative angiography (n=712). Survival at 5 and 10 years was 88.3% and 76.6%, respectively. A number of small studies have compared MIDCAB procedures with conventional CABG. A recent propensity-matched analysis of 159 pairs showed comparable rates of procedural complications and similar lengths of hospital stay after LAD revascularization via MIDCAB and sternotomy (88). However, postoperative pain is often increased after a MIDCAB approach. Despite this, full recovery after a MIDCAB procedure appears to be quicker than after sternotomy, with potential improvements in quality of life.

Robotic CABG

In most centers, the term robotic CABG is used to describe a robotic LIMA harvest technique, followed by a hand-sewn off-pump LIMA-LAD anastomosis via a very small (3–4 cm) left anterior thoracotomy without rib excision or spreading. Operative times are generally longer than for CABG procedures through sternotomy, but short-term outcomes are comparable (89). A metaanalysis showed excellent safety and only a 2.5% rate of conversion to sternotomy (90). Concerns about the quality of anastomoses have been raised, but a series of 307 patients showed that 95% of LIMA-LAD conduits were patent among 199 patients with an angiogram before discharge (91). At longer follow-up, graft patency has been in the range of 92% to 97% for LIMA-to-LAD anastomoses through 8 years of follow-up (92,93).

The term robotic CABG may also refer to a robotic totally endoscopic CABG procedure in which the LIMA is both harvested and anastomosed to the LAD by robotic endoscopic techniques. Totally endoscopic CABG procedures have been used to treat isolated LAD lesions and multivessel disease. However, in a single-arm multicenter registry, 13 of 98 patients (13%) with the intention of totally endoscopic CABG needed to be excluded intraoperatively because of failed femoral cannulation or inadequate working space, emphasizing that appropriate patient selection is essential for this very demanding technical procedure (94).

Because it is so technically challenging and has a high rate of conversion to sternotomy of ≈15% to 20% (90), widespread adoption of totally endoscopic CABG procedures awaits the development of easily maneuverable anastomotic devices.

Hybrid Coronary Revascularization

Hybrid coronary revascularization (HCR) consisting of a LIMA-LAD anastomosis through (robotic) MIDCAB plus stenting of remaining non-LAD lesions for patients with multivessel disease has received much attention in recent years. A small randomized trial to assess the safety of the procedure included 200 patients who were randomly assigned to undergo either HCR or CABG. There were no differences in the rates of death, myocardial infarction, stroke, major bleeding, or repeat revascularization at the 1-year follow-up (95). Among centers in the United States, overall short-term complication rates were low and comparable to those of conventional CABG (96). However, particular benefits include higher patient satisfaction and shorter times for patients to return to work. Midterm results over the first years of follow-up have been promising, with reports of rates of major adverse cardiac or cerebrovascular events and survival comparable to those of CABG, although higher rates of repeat revascularization associated with HCR are a potential concern (97,98).

Only carefully selected patients are currently considered candidates for HCR, as shown by a recent analysis of 198 622 patients treated with CABG in the United States between 2011 and 2013, of whom only 0.5% underwent HCR (96). Criteria for HCR therefore include a proximal LAD lesion graftable with a MIDCAB or robotic MIDCAB procedure; a complexity of residual lesions feasible for PCI, for example, intermediate SYNTAX score at most; and no contraindication to dual antiplatelet therapy. Because there is currently no substantiated evidence from largescale randomized controlled trials to support widespread use of HCR as opposed to multiarterial CABG, HCR is currently limited to patients with specific indications (Table 4). Moreover, HCR may be technically and logistically more demanding than CABG or PCI alone, with the option of PCI before CABG, which introduces the issue of preoperative continuation of dual antiplatelet therapy; the option of CABG before PCI, with the potential risk of ischemia in non-LAD lesions; or the option of simultaneous PCI and CABG, which requires a hybrid operating room. The recent National Institutes of Health–funded Hybrid Observational Trial by Puskas and colleagues (100) demonstrated a wide variation in current practice across a network of 11 premier US cardiac surgical centers for patients with hybrid-eligible coronary lesions. There was general agreement among cardiologists and surgeons at these sites as to which of 6669 consecutive

patients who underwent diagnostic coronary angiography could be considered eligible for HCR (n=454, 12.2%). Moreover, among 200 patients who had HCR and 98 who had multivessel PCI, major adverse cardiac or cerebrovascular events were statistically similar through 17.6 months of follow-up, with a nonsignificant trend toward more adverse events in the PCI group during the later months of follow-up. Thus, equipoise is established for a larger prospective randomized trial of HCR versus multivessel PCI in patients with low-SYNTAX-score, hybrid-eligible coronary artery disease. Such a trial has been recently funded by the National Heart, Lung, and Blood Institute and will begin enrollment in late 2017.

Table 4. Proposed Current Indications for Hybrid Revascularization in Patients With Multivessel Disease.

Patients with a low SYNTAX score but an LAD lesion not amenable to PCI
Patients with an indication for CABG requiring complete revascularization but with a contraindication for sternotomy
Patients with a graftable proximal LAD lesion but poor surgical targets in the Cx or RCA that are amenable to PCI
Patients undergoing emergent PCI of a culprit Cx or RCA lesion but with residual disease requiring staged surgical revascularization of the LAD
Patients with a porcelain aorta and no ability to achieve complete revascularization without the use of a proximal anastomosis in whom off-pump revascularization of the LAD can take place with residual lesions being treated by delayed PCI
Patients with a history of pericarditis in whom non-LAD surgical targets are difficult to identify
Patients requiring a redo sternotomy after a previous noncoronary cardiac operation in whom grafting surgical targets in the Cx is high risk for lateral wall dissection

CABG indicates coronary artery bypass grafting; Cx, circumflex; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.
Adapted from Head and colleagues (99) with permission of the publisher.

In a survey of surgeons in the United States, only 10% were in favor of HCR (101), although a more recent survey among 200 cardiologists and surgeons found that three quarters of responders (n=90) believed adoption of HCR will expand in the next decade (102). Therefore, a heart team should weigh the benefits and risks of PCI, CABG, and HCR to decide which treatment is most appropriate for each individual patient with multivessel disease (10). With the most recent randomized trials and large observational studies of PCI with drug-eluting stents versus CABG in multivessel disease showing improved outcomes with CABG,(7,31,37,103)

surgeons will be reassured and confident that CABG is effective and offers increased longevity. Before HCR becomes a standard procedure at centers around the world, surgeons will have to commit to MIDCAB procedures.

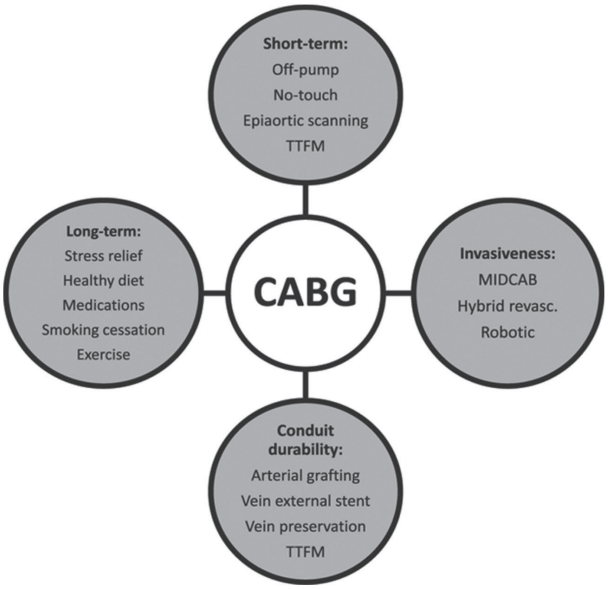


Figure 3. Developments for state-of-the-art coronary artery bypass graft (CABG).
MIDCAB indicates minimally invasive coronary artery bypass; revasc., revascularization; and TTFM, transit-time flow measurement.

Conclusions

Although patients referred for CABG bear increasing cardiovascular risk factors and comorbidities, actual outcomes have significantly improved over the last decades, with low rates of 30-day complications. Although many developments in operative techniques and devices have been established to further improve both shortand long-term outcomes, adoption rates often remain low. The use of multiple arterial conduits remains scarce, mostly because of fear of sternal wound complications and the lack of data from randomized trials; the ART trial, which is currently completing 10 years of follow-up, will provide necessary and long-awaited insights. The weight of data shows similar mortality outcomes with onand off-pump surgery among lowand mixed-risk patients; patients at high risk of morbidity and mortality with conventional CABG benefit most from OPCAB. Minimizing aortic manipulation is directly related to lower rates of stroke after CABG, and no-touch OPCAB may provide the lowest stroke risk. Intraoperative

Doppler graft assessment should be routine, especially in OPCAB. One of the most exciting developments is hybrid revascularization, although evidence for widespread use is not currently available and surgical experience with MIDCAB procedures is still limited. These and other developments have provided the contemporary state-of-the-art CABG procedure (Figure 3).

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Chapter 5

Heart Team decision-making and long-term outcomes for 1000 consecutive cases of coronary artery disease

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ABSTRACT

OBJECTIVES: The Heart Team has been recommended as standard care for patients with coronary artery disease (CAD). However, little is known about the real benefits, potential treatment delays and late outcomes of this approach. Our goal was to determine the safety and feasibility of multidisciplinary Heart Team decision making for patients with CAD.

METHODS: We retrospectively assessed 1000 consecutive cases discussed by the Heart Team between November 2010 and January 2012. We assessed (i) time intervals between different care steps involving the Heart Team; (ii) the distribution of patients according to the complexity of their CAD; and (iii) the 5-year survival as estimated from Kaplan–Meier curves.

RESULTS: Of 1000 case discussions, 40 were repeat cases, resulting in 960 unique cases. The mean age was 65 years, 73% were men, and 29% had diabetes. Native vessel disease was present in 86.4%, of which 69% had simple 1-vessel disease (1VD) or 2-vessel disease (2VD), and 31% had complex left main (LM) or 3-vessel disease (3VD). The time interval between referral by a community hospital and final treatment was less than 6 weeks for 90% of cases. Treatment decisions were delayed in 35% of cases due to a need for additional diagnostic information. For simple 1or 2VD with or without proximal left anterior descending artery involvement, treatment was medical therapy in 6% and 12%, respectively; percutaneous coronary intervention (PCI) in 88% and 85%, respectively; and coronary artery bypass grafting (CABG) in 6% and 3%, respectively. For 3VD disease, treatment was equally split between CABG and PCI (46% for both). PCI was preferred for isolated LM or LM with 1VD (81% vs CABG 16%), whereas CABG was preferred in LM with 2or 3VD (71% vs PCI 19%). The 5-year mortality rate was 16% for 1or 2VD, 17% for 3VD, 3% for isolated LM or with 1VD and 27% for LM with 2or 3VD.

CONCLUSIONS: In this single-centre analysis, the Heart Team approach was feasible, with decision making and treatment by the Heart Team following within a short time after referral. However, the timing of treatment could be further optimized if adequate information and imaging were available at the time of the Heart Team meeting. The final treatment recommendation by the Heart Team was largely in accordance with clinical guidelines.

INTRODUCTION

Decision making about the most optimal treatment for patients with coronary artery disease (CAD) remains a difficult task, particularly since interventional cardiologists, clinical cardiologists and cardiac surgeons are increasingly targeting the same patient population for medical therapy, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

Moreover, the focus on patient groups with a higher risk for adverse outcomes due to advanced age or comorbidities represents a complex new reality in cardiovascular care. These elements have contributed to the need for collaboration among different specialists. Over the last decade, since the publication of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial, a multidisciplinary Heart Team approach has been promoted to provide more patient-centric, evidence-based health care (1).

The Heart Team for CAD established its roots during the conduct of randomized trials. Since the SYNTAX trial, the Heart Team approach has become standard in trials involving complex cardiac conditions with the aim of ensuring accurate patient selection and estimating clinical equipoise between treatments to allow randomization (2). Consequently, there is growing awareness that a multidisciplinary approach to medicine improves the level of care by avoiding individual physician factors (1).

Heart Team decision making has received a Class 1C recommendation in European and American guidelines on myocardial revascularization (3, 4). Despite the assumed advantages of the Heart Team approach over decision making by the individual physician, studies to support this statement are limited. As a result, the Heart Team approach has not yet been widely implemented. The reasons for this are multifactorial, including, amongst others, that (i) some consider that the concept introduces delays in decision making; (ii) meetings held outside the tertiary treating hospitals might not be reimbursed by local health care systems; and (iii) it remains unclear whether decision making is indeed improved by multidisciplinary discussions.

This study evaluates the process of discussing cases by a Heart Team to determine (i) the feasibility of having a Heart Team; (ii) the time interval from referral to treatment; (iii) treatment choices made by the Heart Team; and (iv) real-world long-term results of treatments suggested by the Heart Team. With these data, our

goal was to provide additional understanding of Heart Team decision making that would further support this approach in other institutions and in future clinical guidelines.

METHODS

Study design

This was an observational, retrospective study that included 1000 consecutive cases of patients with CAD discussed by the Heart Team at the Thoraxcenter of the Erasmus University Medical Center between November 2010 and January 2012. Approval from the institutional review board was obtained for this study, and patient informed consent was waived.

Heart Team meetings

The Heart Team meeting takes place daily at 8:30 am, with 30 min allocated for each meeting. The Heart Team comprises a cardiothoracic surgeon, a clinical cardiologist and an interventional cardiologist. In addition, residents of the cardiology or cardiothoracic surgery department, researchers and other health care professionals attend these meetings regularly, which contributes to gaining experience in clinical shared decision making.

At the Heart Team meeting, patients with CAD (with or without concomitant valvular disease) potentially requiring coronary revascularization are discussed. These cases are referred to the Heart Team meeting by cardiologists from community hospitals or cardiologists from our own institution. All patients diagnosed with CAD in our institution, regardless of the complexity of the coronary lesions, are referred for discussion by the Heart Team, except for those patients who undergo an ad hoc PCI procedure. Patients with heart failure, complex valve disease or congenital heart disease are referred to other specialized multidisciplinary teams for additional discussion.

Patient information provided to the Heart Team is listed in an institutional letter (Supplementary Material, Appendix Fig. S1). To ensure that the relevant data are available during the meeting and for reasons of time management, this letter contains baseline characteristics and risk scores determined prior to the Heart Team meeting. During the Heart Team meeting, the coronary angiographic and cardiac echocardiographic images are assessed by the Heart Team. The SYNTAX score was calculated during the meeting only for a select group of patients

with complex CAD to aid the team in making a final treatment decision (1). The decisions made by the Heart Team include CABG, PCI, medical therapy, the need for additional diagnostic information, or the need for input from a different specialty. If additional diagnostic information or input from a different specialty is required, the patient may be discussed again in the Heart Team meeting after this new information becomes available. The decisions for each case are made jointly and are based on the most recent evidence-based treatment recommendations available. After a treatment decision is reached, it is registered on the institutional letter, and the patient and referring cardiologist are informed about the treatment decision and the reasons for that particular decision. The patient's preference is taken into account, and an open, non-autocratic discussion takes place. Patient consent is obtained and, when applicable, the patient is scheduled for the procedure.

Data collection

All cases discussed in the Heart Team meetings are systematically registered in a computerized institutional database. Patients included in this study were extracted from the database. Data were extracted by retrospectively reviewing the institutional letter, the referring letter from the cardiologist and the medical records in our electronic patient information system. In 23 cases, the final treatment received by the patient was missing from our electronic patient information system, which required us to contact the referring community hospital. Information on the vital status of studied patients for up to 5 years was obtained either through the hospital records or the Dutch Civil Registry.

Definitions

Patients with a body mass index >30 kg/m^2 were considered obese. A creatinine level >200 mmol indicated renal impairment. Patients were considered to have hypertension or dyslipidaemia if they were receiving medication to treat it. Left ventricular function was considered normal if the left ventricular ejection fraction (LVEF) was 50–70%, and mild, moderate or severe if the LVEF was 40–49%, 30–39% or <30%, respectively. Summary scores to estimate the procedural risk (e.g. additive EuroSCORE and logistic EuroSCORE) were calculated retrospectively from the information on the institutional letter if the score was not already available.

The clinical presentation of patients ranged from asymptomatic to recent myocardial infarction or out-of-hospital cardiac arrest. These definitions were based on European guidelines (3).

A coronary lesion was considered significant if a >50% stenosis was present in a vessel with a diameter of >1.5 mm. Patients were divided into 3 different groups, depending on the type of CAD. The first group comprised a mix of patients: (i) patients with nonsignificant CAD (the Heart Team found the coronary lesions to be not significant after analysing the coronary angiogram); (ii) patients with unclear involvement of coronary arteries (e.g. due to insufficient information on the coronary angiographic images provided); and (iii) patients with stenosis of the coronary artery from a cause other than arteriosclerosis; for example, spasm or malformation. The second group comprised patients with native vessel CAD. The third group included patients previously treated with CABG who presented with a significant lesion in the saphenous vein graft, internal mammary artery, native vessel or a combination of significant lesions. The second group of patients (e.g. those with native vessel lesions) was further divided into 'simple' versus 'complex' CAD. The group of simple CAD included patients with 1-vessel disease (1VD) or 2-vessel disease (2VD) with and without involvement of the proximal left anterior descending (LAD) artery; and the group of complex CAD included patients with 3-vessel disease (3VD) or left main (LM) disease. The SYNTAX score, if calculated by the Heart Team during the meeting, was used only for patients with complex CAD, who were divided into 3 groups: SYNTAX score 0–22, SYNTAX score 23–32 and SYNTAX score >=33.

Statistical analyses

Discrete variables are reported using percentages and counts of the total sample. Continuous variables are presented as mean with standard deviation or median with interquartile range (Q1– Q3), where appropriate. Five-year survival rates were estimated using Kaplan–Meier methods, and comparisons between groups were made using log-rank testing. Subgroup analyses were performed for subgroups of patients with LM disease or 3VD and within the group of patients with simple coronary disease. A 2 sided P-value of <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Heart Team meetings

Between November 2010 and January 2012, 1000 cases were discussed and 297 meetings took place. A mean of 3.36 cases were discussed at each meeting (median 3, Q1–Q3 2–4). Forty cases were rediscussed, and treatment was initiated only after the second discussion. This process resulted in a total of 960 different

case discussions that resulted in a treatment proposed by the Heart Team. Of the 960 cases, 822 (85.6%) were referred by 22 different community hospitals and 138 (14.4%) were referred by a cardiologist from our own institution.

Table 1. Baseline clinical characteristics presented to the Heart Team.

Characteristics	Patients (n = 960)
Age (years)	65.1 ± 11.0 (960/960)
Male gender	73.0 (701/960)
Comorbid risk factors	
Obesity	27.4 (220/960)
Diabetes	29.0 (278/960)
Hypertension	98.2 (943/960)
Dyslipidaemia	90.6 (870/960)
Tobacco use	20.4 (196/960)
Positive family history	30.7 (295/960)
COPD	12.9 (124/960)
Renal impairment	2.1 (94.7/960)
Cardiovascular history	
No prior cardiovascular events	63.8 (613/960)
Prior PCI	25.8 (248/960)
1 x PCI	18.9 (181/960)
2 x PCI	4.9 (47/960)
3 x PCI or more	2.1 (20/960)
Prior CABG	8.0 (77/960)
1 x CABG	7.9 (76/960)
2 x CABG	0.1(1/960)
Prior other cardiac procedure (excluding CABG)	1.1 (11/960)
Prior heart failure	6.1 (59/960)
Peripheral vascular disease	11.1 (107/960)
Recent myocardial infarction[a]	24.8 (238/960)
Left ventricular function	
Normal	77.3 (742/958)
Mild	12.5 (120/958)
Moderate	5.4 (52/958)
Severe	4.6 (44/958)
Risk scores	
Additive EuroSCORE	4.0 ± 3.0 (954/960)
Logistic EuroSCORE	4.6 ± 5.6 (954/960)

Values are shown as mean ± SD (n) or% (n/N).

[a]Occurred in the last 3 months.

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 2. Disease-specific and anatomical characteristics at presentation to the Heart Team.

Characteristics	Patients (n = 960)
Presentation	
Asymptomatic or atypical symptoms	15.7 (151/960)
Stable angina	35.3 (339/960)
Unstable angina	23.5 (226/960)
NSTEMI	14.2 (137/960)
STEMI	3.2 (31/960)
Congestive heart failure	7.6 (73/960)
Out-of-hospital cardiac arrest	2.0 (20/960)
Coronary artery disease	
Undefined or non-significant	5.5 (53/960)
De novo	86.5 (830/960)
Simple	69.4 (576/830)
1VD or 2VD—non-proximal LAD	77.4 (446/576)
1VD or 2VD—proximal LAD	22.6 (130/576)
Complex	30.6 (254/830)
3VD only	64.6 (164/254)
Left main, any	35.4 (90/254)
Left main, isolated or with 1VD	35.6 (32/90)
Left main, with 2VD or 3VD	64.4 (58/90)
Previous CABG	8.0 (77/960)
Bypass graft (SVG or IMA)	48.1 (37/77)
Native vessel	33.8 (26/77)
Both bypass graft and native vessel	18.2 (14/77)
SYNTAX score	23.2 ± 10.4 (156/254)
Low (0-22)	51.9 (81/156)
Intermediate (23-32)	29.5 (46/156)
High ≥(33)	18.6 (29/156)

Values are shown as mean ± SD (n) or % (n/N). 1VD, single-vessel disease; 2VD, 2-vessel disease; 3VD, 3-vessel disease; CABG, coronary artery bypass grafting; IMA, internal mammary artery; LAD, left anterior descending; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; SD, standard deviation; SVG, saphenous vein graft.

Patient population

The mean age of the population was 65.1 ± 11.0 years, and 73% were men (Table 1). Diabetes was present in 29% of patients, and 23% of patients had left ventricular dysfunction. The mean additive EuroSCORE was 4.0% ± 3.0%, and the logistic EuroSCORE was 4.6% ± 5.6%.

The majority of patients presented with stable or unstable CAD, or a recent non-ST-segment elevation myocardial infarction (Table 2). Group 1 included 53 patients (5.5%) in whom the involvement of the coronary artery was not clear at presentation to the Heart Team, who had coronary artery spasm or malformation, or who had no

CAD at all (Fig. 1). Group 2 included 830 patients (86.5%) who presented with native vessel CAD. Group 3 included 77 patients (8%) with a history of CABG. Among the patients with native vessel CAD, the majority of patients presented with simple CAD either with or without involvement of the LAD artery (69.4%). The other 30.6% of the patients had complex CAD with a mean SYNTAX score of 23.2 ± 10.4.

Time intervals

Patients referred by the cardiologists from Erasmus MC were discussed at the meeting held the same day as the referral or the day thereafter and received treatment a median of 10 days (Q1– Q3 1–27) after discussion by the Heart Team.

For patients who were referred to the Heart Team from community hospitals, the Heart Team meeting took place a median of 2 days (Q1–Q3 1–4) after the referral (Fig. 2). It took a median of 16 days (Q1–Q3 4–27) from referral to treatment. In the subgroup of cases with simple CAD, it took a median of 16 days (Q1–Q3 4–26) from referral to treatment, whereas for complex CAD it took a median of 14 days (Q1–Q3 5–35). Treatment was performed within 6 weeks of referral in 90.0% of the cases: 93.2% for simple CAD and 80.2% for complex CAD. Treatment within 2 weeks of referral was performed in 48.0% of the cases: 46.5% for simple CAD and 51.4% for complex CAD. In only 27 of the 822 externally referred patients (3.3%), the time from referral to treatment took more than 3 months, which was explained by the need for further evaluation of another cardiac condition in 11 cases (1.3%), a requested delay by the patient in another 11 cases (1.3%) and another non-cardiac condition that required investigation or treatment before revascularization in 5 cases (0.6%).

Heart Team decisions

The Heart Team requested an additional investigation in more than one-third of the case discussions before deciding on a final treatment recommendation (Table 3). Invasive cardiac imaging was required in 29.2% of the cases. In 4.3% of the cases, it was necessary to perform non-invasive cardiac imaging to assess myocardial viability or concomitant valve disease.

The majority of patients in Group 1 received medical therapy. After further investigation, 18.8% underwent PCI and 3.7% had CABG (Fig. 3). Of the patients in Group 2 who presented with native 1VD or 2VD, PCI was the recommended treatment in 84.7% of patients without proximal LAD involvement and in 87.6% of patients with proximal LAD involvement, whereas CABG was recommended in only 2.6% and 6.1%, respectively. Patients with isolated LM disease or LM plus 1VD underwent PCI in 81.2% of cases and CABG in 15.6%. Patients with LM disease and

2VD or 3VD underwent PCI in 18.9% of cases and CABG in 70.6%. There was an equal split of 45.7% PCI and 45.7% CABG in patients with 3VD without LM disease, whereas 8.5% of patients received medical therapy. Patients in Group 3 with a previous CABG underwent PCI in 79.2% of cases and received medical therapy in 19.4%, whereas only 1 redo CABG was performed.

Long-term survival

Twenty-six patients were lost to follow-up during a median time of 4.6 years (Q1–Q3 4.2–5.0). The 5-year mortality rate of patients with simple native-vessel CAD was comparable for 1VD or 2VD with proximal LAD involvement (16.4%) and for 1VD or 2VD without proximal LAD involvement (15.7%) (P = 0.70) (Fig. 4A). Patients with isolated LM or in combination with 1VD showed the lowest mortality rate (3.4%), whereas those patients with LM and additional 2VD or 3VD had the highest mortality rate (26.9%) after 5 years (Fig. 4B). Patients with 3VD without LM disease had a mortality rate of 17.1% after 5 years of follow-up.

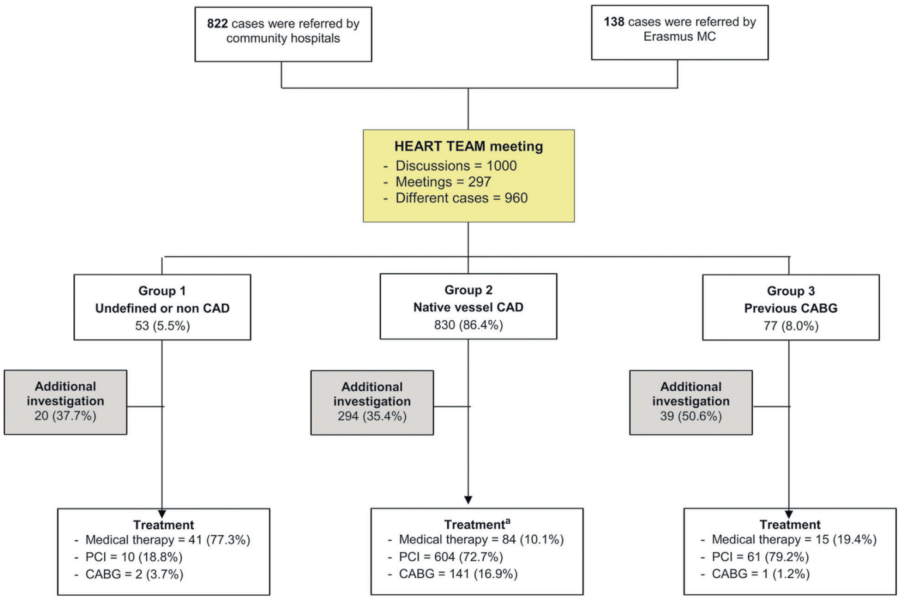


Figure 1. Patient flowchart according to clinical presentation. [a]One patient was lost to follow-up. Additional investigation: clinical evaluation (comorbidity evaluation or other specialist opinion), non-invasive cardiac imaging (myocardial ischaemia test, dobutamine stress echocardiography, magnetic resonance imaging and multislice computed tomography) and invasive cardiac imaging (intravascular ultrasound, coronary angiography and coronary angiography with fractional flow reserve). CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

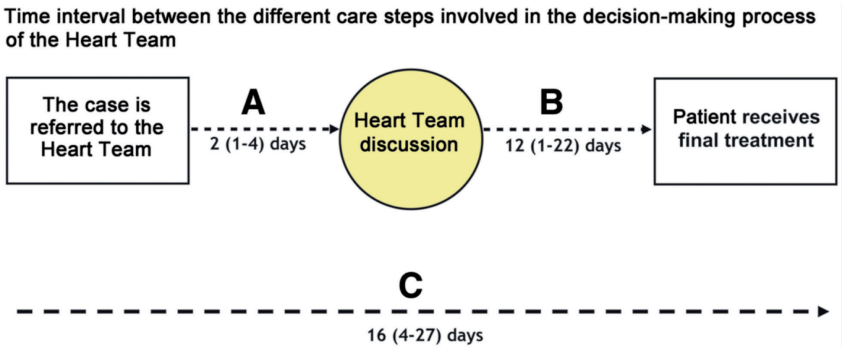


Figure 2. Time from referral from community hospitals to the Heart Team discussion and treatment. Times represent referral by the community hospital to the Heart Team discussion **(A)**; from the Heart Team discussion to final treatment **(B)**; and from referral to final treatment including the discussion in the Heart Team meeting **(C)**. The median of time in days and its corresponding interquartile range (Q1–Q3).

DISCUSSION

This study includes all of the steps of care of a large group of patients with CAD discussed by a real-world Heart Team. By analysing 1000 cases discussed by the Heart Team from referral to long-term survival, we found a structured Heart Team approach to be feasible and safe in formulating treatment strategies for patients with CAD. Heart Team discussions have not been widely implemented despite the well-established multidisciplinary approach in other specialties and the fact that the need for Heart Team decision making for CAD is emphasized to promote transparency in decision making, improve the exchange of knowledge, adhere to established guidelines and minimize physician-related bias (5–10). This study provides more evidence to support Heart Team decision making.

From a logistical standpoint, our Heart Team meetings are held early in the morning to avoid interference with other clinical obligations. This timing also allows the treatment recommendations to be performed during the day of the meeting, when necessary, limiting further treatment delays. According to the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines on myocardial revascularization, PCI or CABG should be performed within 6 weeks after angiography for patients with simple CAD and within 2 weeks for patients with a high-risk anatomical configuration (3), based on adverse events that may occur in patients on the wait list for revascularization (11). In this study, revascularization was performed within 6

weeks after referral in the majority of patients, and within 2 weeks in 51.4% of cases with complex CAD. It is important to acknowledge that even with a Heart Team discussion, revascularization can be performed within the recommended time intervals and thus can be considered safe.

Table 3. Heart Team recommendations for additional investigations.

Additional investigation request	Patients (n = 1000)
Any request	35.3 (353/1000)
Clinical evaluation[a]	2.4 (24/1000)
Non-invasive cardiac imaging	4.3 (43/1000)
Myocardial ischaemia test[b]	16.6 (7/43)
Dobutamine stress echocardiography	23.3 (10/43)
Magnetic resonance imaging	32.6 (14/43)
Multislice computed tomography	27.9 (12/43)
Invasive cardiac imaging	29.2 (292/1000)
Intravascular ultrasound	0.3 (1/292)
Coronary angiography	30.1 (88/292)
Coronary angiography with fractional flow reserve	69.5 (203/292)

Values are shown as % (n/N).

[a] Further clinical evaluation when the clinical status of a patient has changed or other non-cardiac comorbidities have been diagnosed during the interval between referral and the Heart Team meeting.

[b] Non-specific request.

In 353 of the cases (35.3%), the Heart Team requested additional diagnostic tests before deciding on a specific treatment recommendation. Due to their complexity, 40 cases (4%) were rediscussed before a decision could be reached. This means that Heart Team decision making can be further optimized by providing adequate information and imaging at the time of the meeting so that a decision can be reached immediately. Nevertheless, even after assessing the patient's record, reviewing the cardiac images, and carefully considering the risks and benefits of revascularization, in 2.4% of cases, there was a need to clinically evaluate the patient. This critical look exemplifies how the multidisciplinary heart team approach promotes customized, patient-centred care. Furthermore, the Heart Team aims to increase agreement among surgeons and cardiologists, which enables a more consistent tailor-made final treatment recommendation and a bidirectional exchange of information and preferences between physicians, patients and their families. Indeed, numerous studies have shown that multidisciplinary teams in oncology changed the initial management plan because of new insights or newly clarified diagnostic information and improved patient satisfaction by providing a shared decisionmaking process (12).

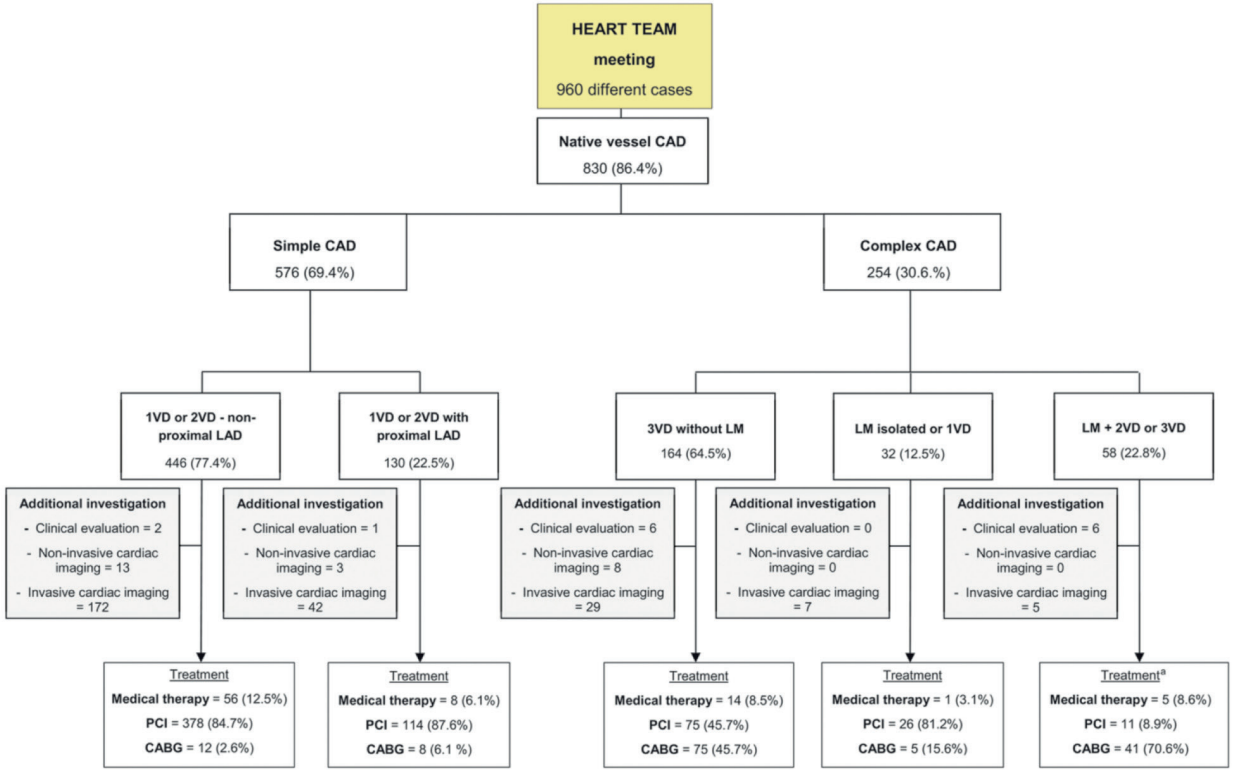


Figure 3. Patient flowchart according to complexity of disease. [a]One patient was lost to follow-up. 1VD, single-vessel disease; 2VD, 2-vessel disease; 3VD, 3-vessel disease; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending; LM, left main; PCI, percutaneous coronary intervention.

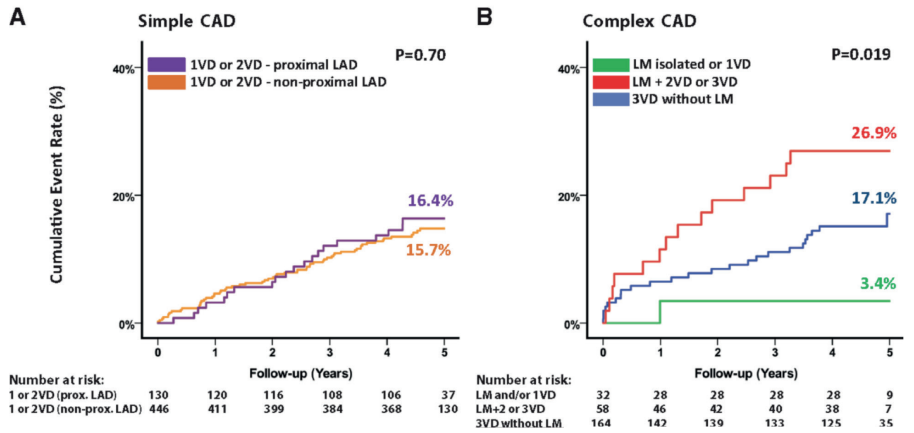


Figure 4. All-cause death after Heart Team proposed treatment for patients with native vessel CAD. (A) An analysis of patients with simple CAD; **(B)** an analysis of patients with complex CAD. 1VD, single-vessel disease; 2VD, 2-vessel disease; 3VD, 3-vessel disease; CAD, coronary artery disease; LAD, left anterior descending; LM, left main.

Other studies have explored different aspects of the Heart Team decision making. Denvir et al. (13) assessed variations in decisions to revascularize patients with CAD between specialists and found that there was a statistically significant poor agreement between cardiac clinical specialists in the choice of treatment offered to patients. An open discussion appeared to improve agreement by providing more evidence to support the Heart Team discussions and thereby improving the decision making. This finding has been demonstrated by Sanchez et al. (14), who found that the decision to revascularize, as provided by the Heart Team was appropriate according to the Appropriate Use Criteria in 99.3% of cases. Importantly, our data add to the existing literature on using a Heart Team by showing that the treatment recommendation of CABG, PCI or medical therapy as provided by the Heart Team was consistent with clinical guideline recommendations (3). Patients with simple native vessel CAD most often underwent PCI, whereas patients with more complex diseases increasingly underwent CABG. Only 1 patient who presented with angina after previous CABG underwent redo CABG; the remaining patients received either medical therapy or PCI, which is the recommended strategy in patients with atherosclerotic graft disease (3, 4). Several studies found that the Heart Team treatment suggestion was implemented in >90% of the cases (15, 16). In cases in which the Heart Team decision was not implemented, this was usually due to factors unknown at the time of the discussion (15, 16). However, some patients require urgent PCI while awaiting CABG, which may cause deviations from the Heart Team suggestion.

Non-primary PCI without on-site surgical backup is controversial and may lead to physician-related bias. Success and failure in the care of patients, especially those with multivessel CAD, hinge on communication between surgeons and cardiologists. Therefore, clear protocols by national regulatory bodies on which patient should be discussed within a Heart Team are warranted. Patients who received revascularization without a documented Heart Team decision will only be covered legally if the procedure is performed according to national guidelines.

Our analysis provides novel insights into the real-world, long-term survival of patients treated according to the Heart Team decisions. In the SYNTAX trial, the 5-year mortality rate in the randomized cohort of patients with LM or 3VD was 11.4% after CABG and 13.9% after PCI. Specifically, patients with 3VD had a mortality rate of 9.2% vs 14.6% after CABG and PCI, respectively (17), which is lower than the 17.1% mortality rate in our study. However, our real-world cohort also included patients who would otherwise not be randomized in the SYNTAX trial; indeed patients in the SYNTAX registries had a 5-year mortality rate of 12.6% (CABG Registry) and 30% (PCI Registry) (18), respectively. Thus survival of the entire SYNTAX cohort will be higher than that of the randomized cohort and more comparable to that of our analysis. Moreover, only patients with de novo CAD were included in the SYNTAX trial; whereas we included a large percentage of patients with a history of PCI, which may increase the risk of death during the follow-up period.

Limitations

This study is retrospective; therefore, several inherent limitations should be considered. For example, some information may not have been recorded in patient records; for example, information on SYNTAX scores was available for only 61.4% (n = 156) of patients with complex disease, so we could not evaluate the distribution of patients to different treatment strategies according to SYNTAX score tertiles. During the enrolment period of the current study, the calculation of the SYNTAX score was not 'standard point of care' in our hospital.

Moreover, data are available only on decisions made by the Heart Team, so we were unable to assess whether the treatment decisions suggested by the individual Heart Team members were changed during the Heart Team discussion. In addition, although we included 1000 case discussions, the complexity of disease was variable so the groups of patients with specific coronary complexities were too small to compare 5-year survival rates with different treatment strategies.

CONCLUSIONS

The Heart Team approach is feasible and provides transparency for decision making. Decision making and treatment by the Heart Team followed within a short time after patient referral, suggesting that the Heart Team does not compromise maximum waiting times. However, the flow of patients can be further optimized if adequate information and imaging files are available at the time of the Heart Team meeting. The final treatment recommendation by the Heart Team was largely in accordance with clinical guidelines.

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SUPPLEMENTAL MATERIAL

Supplementary figure 1. Heart Team sheet cardiothoracic surgery.

Erasmus MC
University Medical Center Rotterdam

Heart Team Sheet Cardiothoracic Surgery
Department of Cardiothoracic Surgery
Erasmus University Medical Center

Patients Name: _____ Date: _____
Identification number: _____ ☐ Male ☐ Female Cardiologist: _____
Date of birth: _____ Referring hospital: _____
Profession: _____ Is patient admitted? ☐ NO ☐ YES

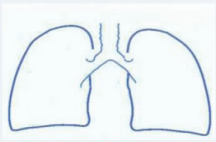
Medical history: _____ Medical complaints: _____

Nicotine abuse ☐ Family history CAD ☐ NYHA classification I ☐ II ☐ III ☐ IV ☐
Hypertension ☐ Hypercholesterolemia ☐

Medication: _____
Allergies: _____

Weight: ____ FEV1: ____ RR: ____
Height: ____ VC: ____
ECG: _____
Auscultation: _____
Ergometry: _____

Hb ____ Creat. ____ ESR ____ WBC ____ AST ____ Glucose ____ Blood type ____
Ht ____ Urea ____ CRP ____ Urine ____ ALT ____ Tromb. ____ Rh. ____



Age		Emergency		Diabetes	
Reoperation		Unstable AP		Prior CVA	
Endocarditis active		Creatin.		Other than CABG	
Critic pre-op state		COPD		Surg Thor. Aorta	
Recent MI		Ex. Art. Path		Postinf VSD	
Pulm. Hypert.		Neuro. Dysf.			

LV Function: ☐ Good ☐ Decreased ☐ Average ☐ Bad
Dominance: ☐ Left ☐ Right

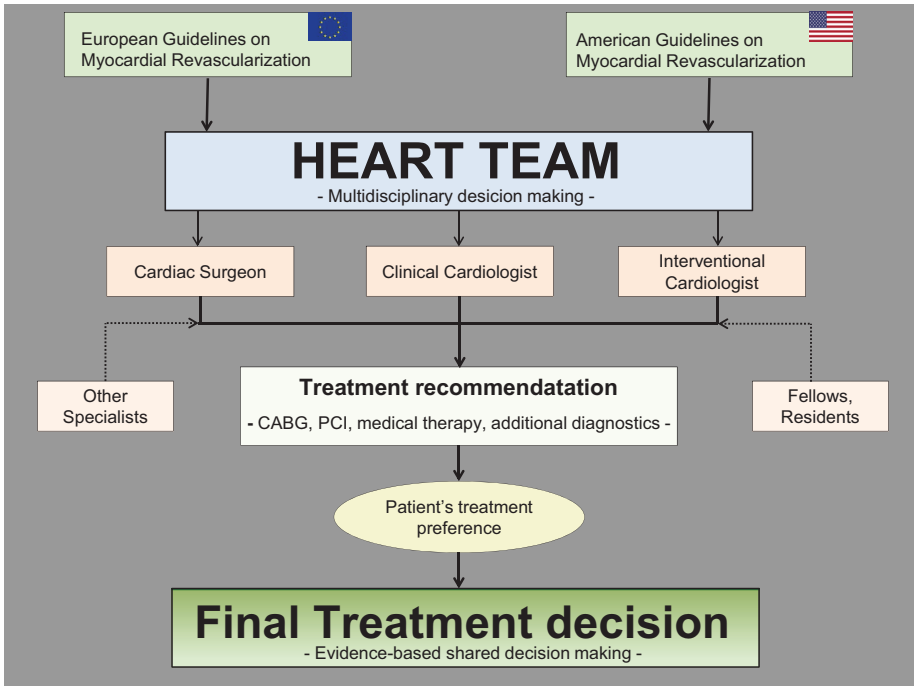
			Pressure	Sat.		Pressure	Sat.
Main	PLCX	VCS			LA		
LAD	RCA	VCI			LV		
Diag.	RDP	RA			AO		
IM	PLr	AP			EF		
Cx	LIMA	APS			CO		
MOI	RIMA	APD			CI		
MOII	Venous	Wedge			PVR		
					Shunt		

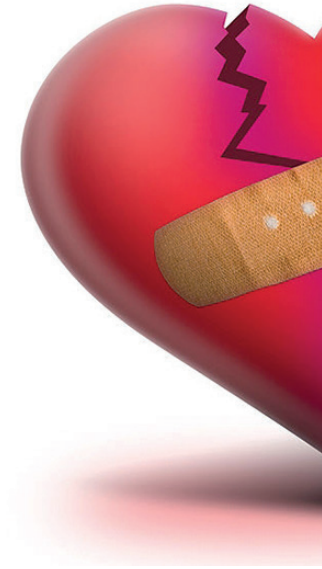
Ultrasound Ao-valve: _____
Mitral valve: _____
LV Function: ☐ Good ☐ Decreased ☐ Average ☐ Bad
Other: _____

Date	Recommendation(s)/Additional exams	Ready	Urgency
1. _____	_____	☐ NO ☐ YES	1 2 3
	_____		
Discussed by	_____	☐ NO ☐ YES	
2. _____	_____		

CAD, coronary artery disease; NYHA, New York Heart Association; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; RR, Riva-Rocci (bloodpressure); VC, vital capacity; Hb, hemoglobine; Ht, hematocrit; Creat, creatinine (measure renal clearance); ESR, erythrocyte sedimentation rate; CRP, C-reactive Protein; WBC, white blood count; AST, aspartate aminotransferase (liver enzyme); ALT, alanine aminotransferase (liver enzyme); Tromb, trombocytes; Rh., rhesus factor; MI, myocardial infarction; AP, angina pectoris; COPD, chronic obstructive pulmonary disease; Ex. Art. Path, extra-arterial pathology; CVA, cerebrovascular accident, e.g. stroke; CABG, coronary artery bypass grafting; Surg Thor. Aorta, surgery to thoracic aorta; LAD, left anterior descending (coronary artery); Diag, diagonal arterial branch of LAD; IM, intermediary arterial branch; Cx, circumflex artery; MO, margo obtusis; PLCX, postero-lateral branch derived from circumflex artery; RCA, right coronary artery; RDP, ramus descendens posterior; PLr, postero-lateral branch derived from right coronary artery; LIMA, left internal mammarian artery; RIMA, right internal mammarian artery; VCS, superior vena cava; VCI, inferior vena cava; RA, right atrium; AP, arteria pulmonalis; pulmonary artery; APS, arteria pulmonalis sinistra; left pulmonary artery APD, arteria pulmonalis dextra; right Pulmonary artery; LA, left atrium LV, left ventricle; AO, aorta; EF, ejection fraction; CO, cardiac output; CI, cardiax index; PVR, pulmonary vascular resistance.

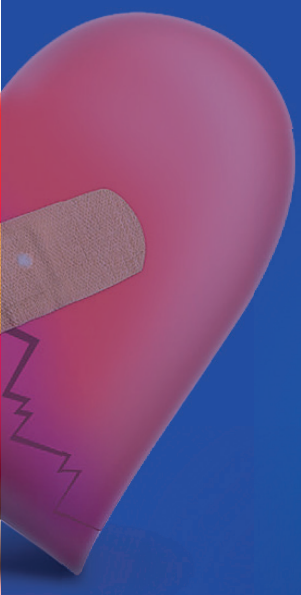
Supplementary figure 2. Heart Team decision making.





Part 2

Bypass Surgery versus Stenting



Chapter 6

Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data

Head SJ, **Milojevic M**, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Fuster V, Flather M, Papageorgiou G, Holm NR, Hlatky M, Hueb WA, Kamalesh M, Kim YH, Mäkikallio T, Mohr FW, Park SJ, Rodriquez AE, Sabik JF, Stables RH, Stone GW, Serruys PW, Kappetein AP.

The Lancet. 2018;391:939-948.

ABSTRACT

BACKGROUND: Numerous randomised trials have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) for patients with coronary artery disease. However, no studies have been powered to detect a difference in mortality between the revascularisation strategies.

METHODS: We did a systematic review up to July 19, 2017, to identify randomised clinical trials comparing CABG with PCI using stents. Eligible studies included patients with multivessel or left main coronary artery disease who did not present with acute myocardial infarction, did PCI with stents (bare-metal or drug-eluting), and had more than 1 year of follow-up for all-cause mortality. In a collaborative, pooled analysis of individual patient data from the identified trials, we estimated all-cause mortality up to 5 years using Kaplan-Meier analyses and compared PCI with CABG using a random-effects Cox proportional-hazards model stratified by trial. Consistency of treatment effect was explored in subgroup analyses, with subgroups defined according to baseline clinical and anatomical characteristics.

FINDINGS: We included 11 randomised trials involving 11 518 patients selected by heart teams who were assigned to PCI (n=5753) or to CABG (n=5765). 976 patients died over a mean follow-up of 3.8 years (SD 1.4). Mean Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score was 26.0 (SD 9.5), with 1798 (22.1%) of 8138 patients having a SYNTAX score of 33 or higher. 5 year all-cause mortality was 11.2% after PCI and 9.2% after CABG (hazard ratio (HR) 1.20, 95% CI 1.06–1.37; p=0.0038). 5 year all-cause mortality was significantly different between the interventions in patients with multivessel disease (11.5% after PCI vs 8.9% after CABG; HR 1.28, 95% CI 1.09–1.49; p=0.0019), including in those with diabetes (15.5% vs 10.0%; 1.48, 1.19–1.84; p=0.0004), but not in those without diabetes (8.7% vs 8.0%; 1.08, 0.86–1.36; p=0.49). SYNTAX score had a significant effect on the difference between the interventions in multivessel disease. 5 year all-cause mortality was similar between the interventions in patients with left main disease (10.7% after PCI vs 10.5% after CABG; 1.07, 0.87–1.33; p=0.52), regardless of diabetes status and SYNTAX score.

INTERPRETATION: CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease. Longer follow-up is needed to better define mortality differences between the revascularisation strategies.

INTRODUCTION

Numerous randomised trials (1–3) have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) with balloon angioplasty, bare-metal stents, or drug-eluting stents for the treatment of multivessel or left main coronary artery disease. In 2009, Hlatky and colleagues[i] reported the results of a pooled analysis of individual patient data from ten randomised trials involving 7812 patients assigned to CABG or PCI with balloon angioplasty or bare-metal stents. In that study, 5 year mortality was 8.4% after CABG and 10.0% after PCI (p=0.12). More recent trials (4–10) comparing CABG with PCI with drug-eluting stents have found similar mortality for the revascularisation strategies. However, to date, no clinical trial has been sufficiently powered to detect a difference in all-cause mortality between CABG and PCI using stents.

To overcome this limitation, we did a pooled analysis of individual-patient data from randomised trials comparing CABG with PCI using stents to examine the comparative effects of these interventions on long-term all-cause mortality in all patients with coronary artery disease and separately in patients with multivessel or left main disease.

Research in context
Evidence before this study

We searched MEDLINE, Embase, and the Cochrane Library up to July 19, 2017, to identify randomised clinical trials comparing coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) using stents. We used the search terms “coronary artery bypass grafting”, “percutaneous coronary intervention”, “stent”, and “random*”. Studies were included if the patients had multivessel or left main coronary artery disease and did not present with acute myocardial infarction, PCI was done with bare-metal or drug-eluting stents and not balloon angioplasty, and more than 1 years’ follow-up for all-cause mortality was available. We identified 12 high-quality trials.

One trial found a survival benefit of CABG over PCI with bare-metal stents for multivessel disease at 6 years’ follow-up. Another trial found better survival at 5 years’ follow-up with CABG than with PCI using first-generation drug-eluting stents in patients with multivessel disease and diabetes. However, these results have not been reproduced in other individual trials with 3–10 years’ follow-up, except in underpowered and hypothesis-generating subgroup analyses. Two pooled analyses of CABG versus PCI with balloon angioplasty or bare-metal stents for multivessel disease

found conflicting results, and what the survival differences are between CABG and PCI remains largely unclear.

Added value of this study

This study is the largest analysis of patients randomly assigned to PCI using stents or to CABG. To our knowledge, this study shows for the first time that all-cause mortality is significantly lower with CABG than with PCI in an overall randomised population of patients with multivessel or left main coronary artery disease. Additionally, the use of individual patient data allowed identification of important subgroups that have a survival benefit from CABG. These subgroups include patients with multivessel disease and diabetes and those with higher coronary lesion complexity (established with the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score). Patients with left main disease had similar survival with PCI and CABG, regardless of diabetes and SYNTAX score.

Implications of all the available evidence

Some patients have specific indications for PCI or CABG, such as coronary complexity too high for PCI or operative risk too high for CABG. In patients with estimated clinical equipoise, as determined by heart teams, consideration of disease type (multivessel or left main), coronary complexity, and diabetes status is crucial because these are important treatment effect modifiers of favourable mortality after CABG versus PCI and should affect decisions on coronary revascularisation in daily practice. However, longer follow-up of randomised trials is needed to better define mortality differences in overall patients and specific subgroups.

METHODS

Study selection and data collection

We searched MEDLINE, Embase, and the Cochrane Library up to July 19, 2017, using the search terms “coronary artery bypass grafting”, “percutaneous coronary intervention”, “stent”, and “random*”. Two researchers (SJH and MM) independently identified randomised trials comparing CABG with PCI in which patients had multivessel or left main coronary artery disease and did not present with acute myocardial infarction, PCI was done with stents (bare-metal or drug-eluting) and not balloon angioplasty, and more than 1 year follow-up for all-cause mortality was available (appendix). Abstracts from meetings were not considered, nor were unpublished trials. Reference lists from potentially relevant articles were checked to ensure no studies were missed.

We contacted the principal investigators of the eligible trials to obtain individual patient data for pooled analyses; data were provided in a standardised spreadsheet. Data were cross-checked against the publication of the primary endpoint and long-term follow-up publications. Several minor inconsistencies were resolved through consensus with trial principal investigators. Baseline and procedural characteristics of individual trials are presented in the appendix with information about missing data for certain characteristics.

We assessed the quality of individual trials using the Cochrane Collaboration's tool for assessing risk of bias (11). Each trial was approved by its local medical ethics committee, and all patients provided written informed consent.

Outcomes and follow-up

To allow a consistent definition of follow-up among trials, the duration of follow-up was calculated from the day of the procedure. If patients died before the procedure, the time from randomisation to death was used to calculate the duration of follow-up.

All-cause mortality was the primary endpoint of this study, with analyses planned in all patients and separately in patients with multivessel disease or left main disease. The multivessel disease group consisted of patients with multivessel disease without left main disease, whereas the left main disease group consisted of patients with any left main disease, irrespective of the number of diseased vessels.

We also planned separate analyses for trials that used bare-metal stents, those that used drug-eluting stents, those that used first-generation drug-eluting stents, and those that used newer-generation drug-eluting stents. First-generation drug-eluting stents released paclitaxel or sirolimus. Newer-generation drug-eluting stents released everolimus, zotarolimus, or biolimus. The VA CARDS trial(7) (Cooperative Studies Program study number 557) was excluded from the separate analyses of first-generation and newer-generation drug-eluting stents because a mixture of these stents was used.

We prespecified subgroups for analyses according to the baseline characteristics sex, age, body-mass index, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous myocardial infarction, leftventricular ejection fraction, and core laboratory-assessed Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (as a measure of lesion complexity) (12).

Post-hoc subgroup analyses were done according to SYNTAX score tertiles in the groups of patients with or without diabetes. In all trials, a Clinical Events Committee adjudicated the events.

Statistical analysis

A team consisting of three epidemiologists and statisticians (MM, EB, and GP) did the statistical analyses. All analyses were done by intention to treat. Baseline, procedural, and outcome data for individual patients were pooled. Continuous variables are presented as mean (SD) and were compared with *t* tests; discrete data are presented as frequencies and were compared with χ^2 tests.

We pooled data from all trials to provide unadjusted Kaplan-Meier estimates of all-cause mortality at 5 years follow-up and for landmark analyses at 30 days and between 31 days and 5 years. Subgroup analyses were done with follow-up data at 5 years only. PCI and CABG were compared with random-effects Cox proportionalhazards models stratified by trial and with inclusion of a γ frailty term to account for heterogeneity between trials. Trial heterogeneity is captured in random-intercept frailty terms, which quantify trial-specific deviation from the average hazard ratio (HR). Frailties are unobserved factors, distributed as γ random variables with a mean of 1 and variance (θ). Hence, the variance of the frailty terms represents heterogeneity in baseline risk between trials. The significance of the variance parameter was assessed with the likelihood ratio test. The proportional hazards assumption in the Cox model for the overall group was assessed by visual inspection of the scaled Schoenfeld residuals over a Kaplan-Meier transform of time, as well as with the corresponding test for the correlation of the Schoenfeld residuals with time, and was not violated (p=0.12). Nevertheless, visual inspection of the KaplanMeier curves suggested a time-dependent variance in the HR of PCI versus CABG and, therefore, models that allowed for a time-varying HR were also done. For these models, we assumed a single cutoff point, allowing the HR to have different values before and after the cutoff. The cutoff was selected on the basis of visual inspection of the scaled Schoenfeld residuals. Subgroup analyses according to baseline clinical, procedural, and anatomical characteristics were also done with the Cox models.

Table 1: Baseline, procedural, and discharge data of randomised cohorts.

	PCI (n=5753)	CABG (n=5765)	p value
Age (years)	63·6 (9·8; 5753)	63·7 (9·9; 5765)	p=0·72
Sex			
Female	23·9% (1373/5753)	23·8% (1371/5765)	p=0·91
Male	76·1% (4380/5753)	76·2% (4394/5765)	p=0·91
Body-mass index >30 kg/m^2	28·1% (1548/5506)	28·3% (1558/5511)	p=0·82
Current smoker	22·3% (1274/5701)	22·3% (1273/5703)	p=0·97
Diabetes	38·5% (2215/5753)	37·7% (2171/5765)	p=0·35
Insulin treated	12·9% (545/4234)	11·9% (504/4245)	p=0·16
Hypertension	67·6% (3880/5739)	68·1% (3913/5748)	p=0·59
Hypercholesterolaemia	69·5% (3982/5726)	67·3% (3862/5735)	p=0·0112
Peripheral vascular disease	8·2% (424/5158)	8·5% (440/5164)	p=0·58
Carotid artery disease	7·8% (161/2072)	8·1% (168/2074)	p=0·69
Previous TIA or CVA	5·4% (218/4052)	6·2% (253/4054)	p=0·098
Previous myocardial infarction	28·0% (1438/5138)	27·5% (1417/5156)	p=0·57
Left-ventricular ejection fraction			
Moderate (30–49%)	15·2% (807/5303)	14·3% (779/5430)	p=0·20
Poor (<30%)	0·9% (49/5303)	1·0 (54/5430)	p=0·71
Unstable angina pectoris	34·6% (1786/5158)	34·2% (1767/5160)	p=0·68
Three-vessel disease*	58·6% (2460/4201)	61·8% (2594/4197)	p=0·063
Left main disease	38·8% (2233/5753)	38·9% (2245/5765)	p=0·89
SYNTAX score	26·0 (9·3; 4081)	26·0 (9·8; 4057)	p=0·91
0–22	37·6% (1533/4081)	39·1% (1585/4057)	p=0·16
23–32	41·1% (1677/4081)	38·1% (1545/4057)	p=0·0053
≥33	21·3% (871/4081)	22·8% (927/4057)	p=0·10
Type of stent used in PCI†			
Bare-metal stent	26·6% (1490/5610)	..	..
Drug-eluting stent	73·4% (4120/5610)	..	..
First-generation	39·2% (2199/5610)	..	..
Newer-generation	34·2% (1920/5610)	..	..
Number of stents used in PCI	3·1 (2·0; 4935)	..	..
CABG procedure			
Left internal mammary artery	..	96·2% (4574/4753)	..
Bilateral internal mammary artery	..	18·7% (771/4122)	..
Off-pump	..	27·5% (1085/3945)	..
Medication at discharge			
Aspirin	97·3% (4487/4612)	95·5% (3814/3994)	p<0·0001
Thienopyridine	96·7% (4479/4630)	45·1% (1815/4026)	p<0·0001
Dual antiplatelet therapy	95·1% (4384/4612)	44·0% (1759/3994)	p<0·0001
Statin	88·1% (3052/3464)	84·0% (2843/3384)	p<0·0001
β blocker	79·1% (2741/3464)	76·2% (2557/3356)	p=0·0040
ACE inhibitor or ARB	63·7% (2205/3464)	46·9% (1588/3383)	p<0·0001
Calcium-channel blocker	27·7% (959/3463)	21·8% (736/3383)	p<0·0001

Data are mean (SD; n) or % (n/N). PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischaemic attack; CVA, cerebrovascular attack; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. *Of the group of patients with multivessel disease. †Data are only for patients who underwent PCI; the type of drug-eluting stent used was not available for one patient enrolled in the VA CARDS trial (7).

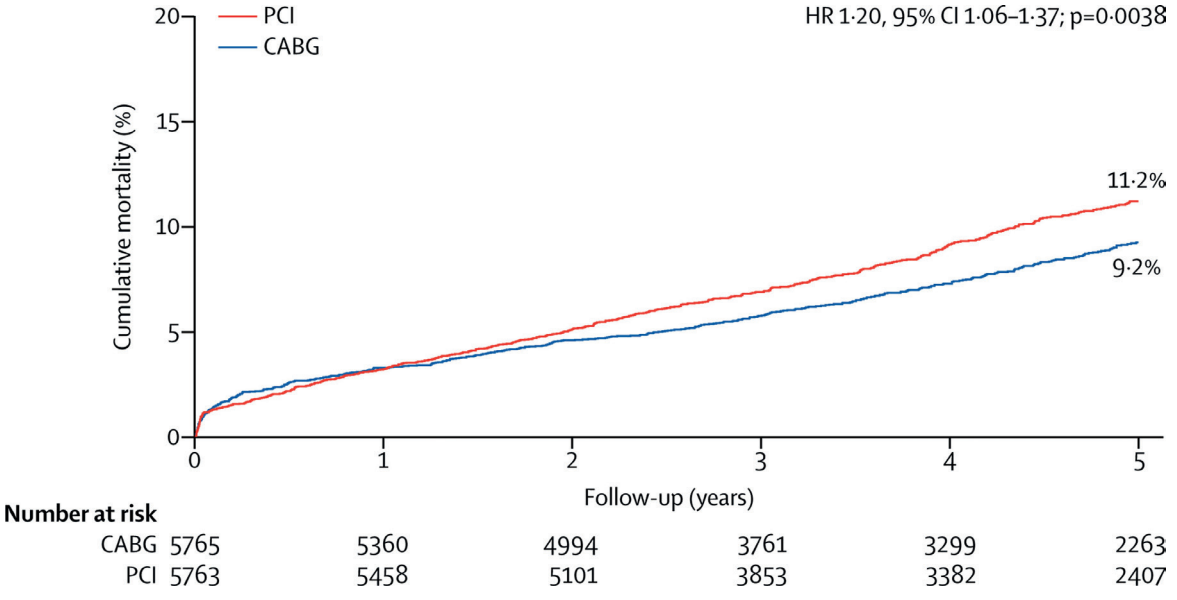


Figure 1. Mortality after CABG versus after PCI during 5 years' follow-up

Kaplan-Meier estimates are from the overall pooled patient population. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HR, hazard ratio.

Table 2. 5 year all-cause mortality in all patients and according to disease type.

	All patients				Multivessel disease				Left main disease			
	CABG (n=5765)	PCI (n=5753)	HR (95% CI; p value)	Heterogeneity	CABG (n=3520)	PCI (n=3520)	HR (95% CI; p value)	Heterogeneity	CABG (n=2245)	PCI (n=2233)	HR (95% CI; p value)	Heterogeneity
All	9·2% (437/5765)	11·2% (539/5753)	1·20 (1·06–1·37; p=0·0038)	θ=0·39; p<0·0001	8·9% (279/3520)	11·5% (365/3520)	1·28 (1·09–1·49; p=0·0019)	θ=0·40; p<0·0001	10·5% (158/2245)	0·7% (174/2233)	1·07 (0·87–1·33; p=0·52)	θ=0·0845; p<0·0001
Diabetes	..	..	$p_{interaction}$=0·0077	..	..	..	$p_{interaction}$=0·0453	..	..	..	$p_{interaction}$=0·13	..
Yes	10·7% (185/2171)	15·7% (278/2215)	1·44 (1·20–1·74; p=0·0001)	θ=0·11; p<0·0001	10·0% (134/1622)	15·5% (207/1644)	1·48 (1·19–1·84; p=0·00037)	θ=0·16; p<0·0001	13·4% (51/549)	16·5% (71/571)	1·34 (0·93–1·91; p=0·11)	θ=0·0536; p=0·0177
No	8·4% (252/3594)	8·7% (261/3538)	1·02 (0·86–1·21; p=0·81)	θ=0·0884; p<0·0001	8·0% (145/1898)	8·7% (158/1876)	1·08 (0·86–1·36; p=0·49)	θ=0·0992; p<0·0001	9·6% (107/1696)	8·8% (103/1662)	·94 (0·72–1·23; p=0·65)	θ=0·0603; p=0·0027
SYNTAX score	..	..	$p_{interaction}$=0·21	..	..	..	$p_{interaction}$=0·32	..	..	..	$p_{interaction}$=0·38	..
0–22	8·1% (100/1585)	8·8% (105/1533)	1·02 (0·77–1·34; p=0·91)	θ=0·0459; p=0·0092	8·4% (51/691)	10·5% (60/690)	1·11 (0·77–1·62; p=0·57)	θ=0·0523; p=0·0131	8·3% (49/894)	8·1% (45/843)	0·91 (0·60–1·36; p=0·64)	θ<0·0001; p=0·0001
23–32	10·9% (122/1545)	12·4% (163/1677)	1·20 (0·94–1·51; p=0·14)	θ=0·0656; p=0·0031	9·5% (59/775)	14·0% (96/824)	1·50 (1·09–2·08; p=0·0129)	θ=0·0621; p=0·0066	12·7% (63/770)	10·8% (67/853)	0·92 (0·65–1·30; p=0·65)	θ=0·0626; p=0·0093
≥33	11·6% (83/927)	16·5% (117/871)	1·52 (1·15–2·02; p=0·0029)	θ=0·0189; p=0·061	10·9% (38/423)	17·7% (61/397)	1·70 (1·13–2·55; p=0·0094)	θ=0·0252; p=0·050	12·4% (45/504)	15·0% (56/474)	1·39 (0·94–2·06; p=0·10)	θ=0·0217; p=0·065

Data are percentages from unadjusted Kaplan-Meier analyses (number of events/total number of patients), unless otherwise specified. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; HR, hazard ratio; θ, variance.
SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

A two-sided p value of less than 0.05 was considered to indicate statistical significance; we did not adjust for multiplicity. All statistical analyses were done with SPSS software, version 21, or R software, version 3.2.4. Reporting of this individual patient-data, pooled analysis concurs with specific PRISMA guidelines (13). This study is not registered and no protocol has been published.

Role of the funding source

This study was done without funding, although individual trials were sponsored. The decision to submit the manuscript for publication was made by consensus among the principal investigators of the individual trials. Sponsors of the individual trials were involved in data collection in the trials, but were not involved in data analyses, data interpretation, or drafting of this manuscript.

RESULTS

We identified 19 relevant trials in the literature search, of which seven were excluded because patients did not have multivessel or left main disease (n=4), only 54% of PCI procedures were done with a stent (n=1), or follow-up was only available up to 1 year (n=2; appendix). The principal investigators of the remaining 12 trials (4–10,14–18) were contacted to obtain individual patient data for a pooled analysis; one trial (14) involving 105 patients was unable to provide data. All trials were considered to be of high quality according to criteria, despite being unable to mask investigators and patients to treatment allocation (appendix).

In the 11 trials that provided data, 11 518 patients selected by heart teams were randomly assigned to CABG (n=5765) or to PCI (n=5753). PCI was done with bare-metal stents in 1490 patients in four trials (n=3051), with first-generation drug-eluting stents in 2199 patients in four trials (n=4498), and with newer-generation drugeluting stents in 1920 patients in three trials (n=3969; table 1). CABG was done with a left internal mammary artery in 4574 patients in nine trials (n=4753), with a bilateral internal mammary artery in 771 patients in seven trials (n=4122), and off-pump in 1085 patients in seven trials (n=3945). SYNTAX scores were available from six trials and for 8138 patients (CABG: n=4057; PCI: n=4081). The mean SYNTAX score was 26.0 (SD 9.5), with 1798 (22.1%) patients having a SYNTAX score of 33 or higher. Baseline, procedural, and discharge data for the patients are shown in table 1, and data for each trial and treatment crossovers are shown in the appendix. 976 patients died during a mean follow-up of 3.8 years (SD 1.4). 5 year all-cause mortality was 11.2% (539 events) after PCI and 9.2% (437 events)

Table 3. Differences in patient characteristics according to whether trials did PCI with bare-metal or drug-eluting stents.

	Trials with bare-metal stents (n=3051)	Trials with drug-eluting stents (n=8467)	p value	Trials with first-generation drug-eluting stents (n=4300)*	Trials with newer-generation drug-eluting stents (n=3969)*	p value
Age (years)	60.8 (10.1; 3051)	64.7 (9.6; 8467)	p<0.0001	63.8 (9.5; 4300)	65.7 (9.6; 3969)	p<0.0001
Sex						
Female	23.2% (707/3051)	24.1% (2037/8467)	p=0.32	25.3% (1087/4300)	23.9% (948/3969)	p=0.14
Male	76.8% (2344/3051)	75.9% (6430/8467)	p=0.32	74.7% (3213/4300)	76.1% (3021/3969)	p=0.14
Body-massindex>30kg/m^2	22.3% (578/2593)	30.0% (2528/8424)	p<0.0001	32.4% (1388/4290)	25.6% (1010/3939)	p<0.0001
Current smoker	27.5% (843/3049)	20.4% (1704/8355)	p<0.0001	19.6% (833/4260)	21.2% (827/3900)	p=0.064
Diabetes	17.8% (543/3051)	45.4% (3843/8467)	p<0.0001	59.2% (2544/4300)	27.7% (1101/3969)	p<0.0001
Insulin treated	3.4% (48/1396)	14.1% (1001/7083)	p<0.0001	19.0% (816/4299)	6.6% (185/2784)	p<0.0001
Hypertension	51.1% (1558/3051)	73.9% (6235/8436)	p<0.0001	76.5% (3278/4287)	70.1% (2770/3954)	p<0.0001
Hypercholesterolaemia	58.3% (1776/3047)	72.1% (6068/8414)	p<0.0001	75.4% (3230/4285)	69.2% (2727/3938)	p<0.0001
Peripheral vascular disease	7.6% (233/3051)	8.7% (631/7271)	p=0.081	9.2% (396/4300)	7.5% (208/2776)	p=0.0116
Carotid artery disease	5.6% (25/450)	8.2% (304/3696)	p=0.0479	8.2% (148/1800)	8.2% (156/1896)	p=0.99
Previous TIA or CVA	3.3% (47/1438)	6.4% (424/6668)	p<0.0001	5.8% (215/3688)	6.8% (189/2782)	p=0.11
Previous myocardial infarction	42.1% (1285/1766)	21.7% (1570/7243)	p<0.0001	25.8% (1105/4280)	13.9% (384/2768)	p<0.0001
Left-ventricular ejection fraction						
Moderate (30–49%)	16.1% (442/2746)	14.3% (1144/7987)	p=0.0239	15.7% (668/4242)	11.9% (425/3568)	p<0.0001
Poor (<30%)	0.1% (4/2746)	1.2% (99/7987)	p<0.0001	1.6% (66/4242)	0.6% (21/3568)	p<0.0001
Unstable angina pectoris	41.2% (850/2063)	32.7% (2703/8255)	p<0.0001	31.8% (1369/4287)	33.7% (1334/3955)	p=0.067
Three-vessel disease†	41.9% (1280/3051)	70.6% (3774/5348)	p<0.0001	69.4% (2976/4287)	77.2% (679/3969)	p<0.0001
Left main disease	1.0% (29/3051)	52.5% (4449/8467)	p<0.0001	30.5% (1313/4300)	79.0% (3136/3969)	p<0.0001
Follow-up (years)	4.7 (1.0; 2795)	3.5 (1.4; 7726)	p<0.0001	4.0 (1.4; 3830)	3.1 (1.2; 3723)	p<0.0001

Data are mean (SD; n) or % (n/N). TIA, transient ischaemic attack; CVA, cerebrovascular attack; PCI, percutaneous coronary intervention. *The VA CARDS trial7 was excluded from the analysis of first-generation and newer-generation drug-eluting stents because a mixture of these stents was used. †Of the group of patients with multivessel disease.

after CABG (HR 1.20, 95% CI 1.06–1.37; p=0.0038; figure 1, table 2). At 30 days' follow-up, all-cause mortality was 1.3% (76 events) after PCI and 1.4% (78 events) after CABG (0.97, 0.71–1.33; p=0.84). Between 31 days' and 5 years' follow-up, allcause mortality was 10.0% (463 events) after PCI and 8.0% (359 events) after CABG (1.26, 1.09–1.44; p=0.0009). A time-dependent model showed that the risk of mortality was similar for PCI and CABG during the first year of follow-up (0·97, 0·80–1·19; p=0.80), but in favour of CABG beyond 1 year (1.39, 1.17–1.62; p<0.0001; appendix). The estimate of the frailty parameter for heterogeneity was significant (θ=0.39, p<0.0001).

Patients in trials in which drug-eluting stents were used were older, had more comorbidities, and were more likely to have diabetes, left main disease, and three-vessel disease than patients in trials in which bare-metal stents were used (table 3). 5 year all-cause mortality was 8.7% (131 events) after PCI and 8.2% (125 events) after CABG (HR 1.05, 95% CI 0.82–1.34; p=0.72) in trials that did PCI with bare-metal stents (including 3051 patients), and 12.4% (408 events) after PCI and 10.0% (312 events) after CABG (1.27, 1.09–1.47; p=0.0017) in trials that did PCI with drug-eluting stents (including 8467 patients). The type of stent used (bare-metal *vs* drug-eluting) did not interact with the treatment effect ($p_{interaction}$=0.53).

Although there were significant differences in clinical and anatomical characteristics between the trials using first-generation drug-eluting stents and those using newergeneration drug-eluting stents (table 3), the difference in 5 year mortality between PCI and CABG was consistent when analysing the 4300 patients in the trials using firstgeneration drug-eluting stents (13.2% (254 events) after PCI *vs* 11.1% (201 events) after CABG; HR 1.21, 95% CI 1.01–1.46; p=0.0415) and the 3969 patients in the trials using newer-generation drug-eluting stents (10.3% (136 events) after PCI *vs* 7.9% (106 events) after CABG; 1.27, 0.98–1.64; p=0.0658; $p_{interaction}$=0.78).

In subgroup analyses, diabetes was the only baseline characteristic with a significant treatment interaction ($p_{interaction}$=0.0077). In patients with diabetes, PCI was associated with higher 5 year all-cause mortality than was CABG (15.7% (278 events) *vs* 10.7% (185 events); HR 1.44, 95% CI 1.20–1.74; p=0.0001), whereas mortality did not differ between the interventions in patients without diabetes (8.7% (261 events) after PCI *vs* 8.4% (252 events) after CABG; 1.02, 0.86–1.21; p=0.81; table 2, figures 2, 3). Although the interaction was not significant ($p_{interaction}$=0.21), the mortality benefit of CABG over PCI tended to increase with increasing SYNTAX scores (table 2). A similar trend was found in subgroups of patients with or without diabetes (appendix).

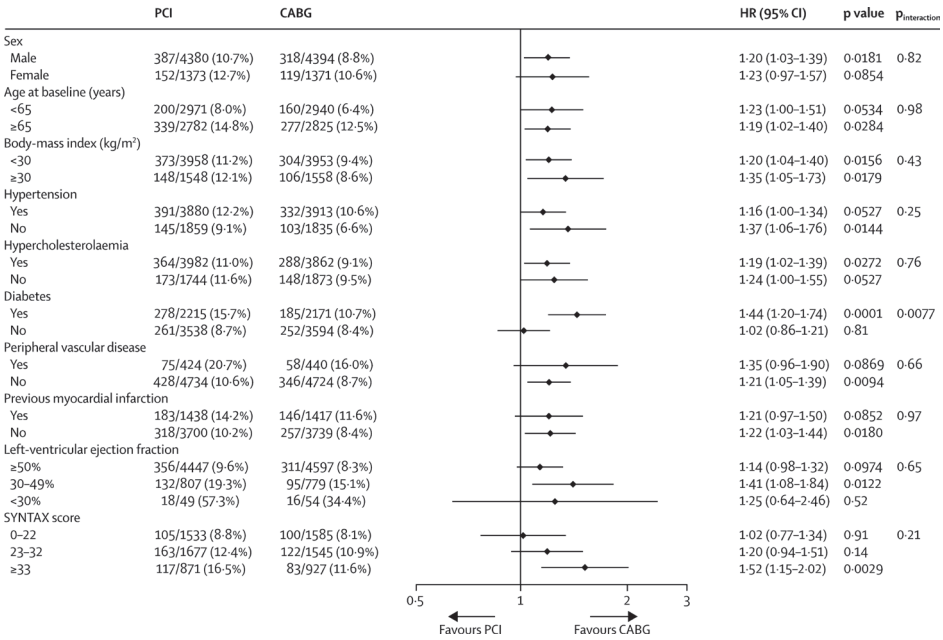


Figure 2. Mortality after CABG versus after PCI during 5 years' follow-up, by subgroup
Kaplan-Meier estimates are from the overall pooled patient population. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HR, hazard ratio; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

644 of 7040 patients with multivessel disease assigned to PCI (n=3520) or to CABG (n=3520) died during a mean follow-up of 4.1 years (SD 1.4). 5 year all-cause mortality in patients with multivessel disease was higher after PCI than after CABG (11.5% (365 events) *vs* 8.9% (279 events); HR 1.28, 95% CI 1.09–1.49; p=0.0019; figure 3, table 2). As observed for the overall patient cohort, the mortality benefit of CABG over PCI in patients with multivessel disease increased with duration of follow-up in time-dependent models (appendix). 5 year all-cause mortality was 15.5% (207 events) after PCI versus 10.0% (134 events) after CABG in the subgroup of patients with multivessel disease who had diabetes (HR 1.48, 95% CI 1.19–1.84; p=0.00037), and 8.7% (158 events) after PCI versus 8.0% (145 events) after CABG in the subgroup of those patients without diabetes (1.08, 0.86–1.36; p=0.49; $p_{interaction}$=0.0453; table 2). The mortality benefit of CABG over PCI increased with increasing SYNTAX scores in patients with multivessel disease (table 2).

322 of 4478 patients with left main disease assigned to PCI (n=2233) or to CABG (n=2245) died during a mean follow-up of 3.4 years (SD 1.4). 5 year all-cause

mortality for patients with left main disease was 10.7% (174 events) after PCI and 10.5% (158 events) after CABG (HR 1.07, 95% CI 0.87–1.33; p=0.52; figure 3, table 2). By contrast with the overall cohort and multivessel disease subgroup, a benefit for CABG over PCI was not seen with longer follow-up in time-dependent models (appendix). Diabetes status did not interact with the treatment effect in patients with left main disease ($p_{interaction}$=0.13). 5 year all-cause mortality was 16.5% (71 events) after PCI versus 13.4% (51 events) after CABG (HR 1.34, 95% CI 0.93–1.91; p=0.11) in the subgroup of patients with left main disease who had diabetes, and 8.8% (103 events) after PCI versus 9.6% (107 events) after CABG (0.94, 0.72–1.23; p=0.65) in the subgroup of those patients without diabetes (table 2). Subgroup analyses according to SYNTAX score in patients with left main disease showed that mortality from PCI and CABG did not differ according to score (table 2).

DISCUSSION

This collaborative analysis of individual patient data from 11 randomised trials is the first large-scale study to compare CABG with PCI with stents. We found that 5 year all-cause mortality was higher after PCI than after CABG in 11 518 patients. In subgroup analyses, CABG only had a mortality benefit over PCI in patients with multivessel disease and diabetes; no difference was seen in patients with multivessel disease without diabetes, nor in patients with left main disease (with or without diabetes). Coronary lesion complexity, assessed with the SYNTAX score, was an important effect modifier in patients with multivessel disease, but did not appear to modify treatment effect in those with left main disease.

The relative benefits of CABG versus PCI with stents in terms of outcomes are highly debated, particularly each time stent design is enhanced. Improvements in stent design have led to inclusion of higher-risk patients with more complex disease, such as three-vessel or left main disease, in randomised trials. This higher-risk profile is also reflected in our data, wherein 5 year allcause mortality in both the CABG and PCI cohorts was higher in more recent trials with drug-eluting stents than in earlier trials with bare-metal stents, but a larger relative benefit of CABG over PCI was most likely due to more complex coronary artery disease.

In all of the included trials, both an interventional cardiologist and a cardiac surgeon had to assume clinical equipoise between PCI and CABG for patients to be randomised. Some patients were not eligible for inclusion in the selected trials because of having coronary lesion complexity too severe to be treated with PCI

or operative risk deemed too high for CABG (19). The results of this analysis are not generalisable to the entire population of patients with coronary artery disease that require revascularisation. Therefore, heart team decision making is crucial to recommend the best revascularisation strategy for an individual patient (20).

The mortality benefit of CABG over PCI in the overall group was retained over a variety of patient baseline characteristics. However, the presence of diabetes was an important modifier, as shown in previous analyses.[1] The benefit of CABG in patients with diabetes might be attributed to more effective revascularisation of diffuse, complex coronary disease. This hypothesis is consistent with the findings of the subgroup analysis according to SYNTAX score. In the total cohort, a step-wise increase in the difference between CABG and PCI was observed with increasing SYNTAX scores. Other studies (21) have also identified sex as an effect modifier, but we did not find a significant treatment-by-sex interaction for 5 year mortality. Patients with multivessel disease had lower mortality with CABG than with PCI, consistent with the SYNTAX trial that compared CABG with PCI using first-generation drug-eluting stents (22,23). The BEST trial (8), in which secondgeneration everolimus-eluting stents were used to treat multivessel disease, also found that CABG was associated with a lower incidence of major adverse cardiac or cerebrovascular events, driven by a reduced incidence of myocardial infarction and repeat revascularisation. Large real-world registries have applied propensity score matching to compare CABG with PCI using drug-eluting stents for multivessel disease to find differences in survival with larger sample sizes (24,25). The ASCERT study (25), the largest of such analyses, reported an adjusted 4 year mortality of 16.4% for CABG and 20.8% for PCI with first-generation drug-eluting stents in a cohort of patients aged 65 years or older; mortality was consistent across multiple subgroups. Notably, the survival curves of CABG and PCI in this study are similar to those of the ASCERT study: PCI shows a benefit within the first year of followup, but a larger benefit is seen with CABG than with PCI with longer follow-up. We showed that this reversal of risk resulted in a benefit for CABG over PCI at a mean follow-up of 4.1 years, which might become larger with longer follow-up given that the HR favoured CABG at later follow-up in time-varying models.

In the SYNTAX trial (26), 5 year mortality was similar for CABG and PCI with paclitaxel-eluting, first-generation drug-eluting stents in patients with left main disease. Two major trials (9,10) have since focused on finding the optimal revascularisation strategy for left main disease and have reported conflicting outcomes of CABG versus PCI. The EXCEL trial (10) reported that PCI was non-inferior to CABG after 3 years, whereas the NOBLE trial (9) did not show noninferiority for PCI versus CABG at 5 years. The

differences in timing and composition of the primary endpoints make comparing these trials difficult and presumably explain the apparent difference in results. 3 year individual endpoints in the NOBLE trial were later confirmed to be similar to those in the EXCEL trial (27). In our pooled analysis of data for patients with left main disease from four different trials, mortality was similar after CABG and PCI at 5 years' follow-up. Unlike for patients with multivessel disease, the similarity in mortality in patients with left main disease was consistent in a subgroup analysis according to diabetes status, although this difference might be due to the smaller sample size in the diabetic subgroup of patients with left main disease. Coronary complexity did not affect mortality in patients with left main disease, although patients with a high SYNTAX score were relatively under-represented because of specific inclusion criteria (eg, in the EXCEL trial) and a preference of heart teams for CABG (19). Therefore, the degree of complexity should still be considered when proposing a specific treatment for individual patients with left main disease. Patients with a complex left main lesion and three-vessel disease with a high SYNTAX score might still benefit from CABG in terms of mortality, as well as incidence of myocardial infarction and repeat revascularisation, whereas patients with a non-complex lesion and one-vessel or two-vessel disease might be excellent candidates for PCI. Clinical guidelines have not been revised since the release of data from the EXCEL and NOBLE trials. Based on existing data of similar mortality with the two interventions, the indication for PCI with contemporary drug-eluting stents might be broadened to patients with more complex left main disease (eg, intermediate SYNTAX scores). However, given that only 978 patients with left main disease in our cohort had high SYNTAX scores, additional data are required before PCI can be routinely recommended in patients with complex left main disease. Longer follow-up is essential to better define differences in survival between CABG and PCI, because landmark analyses from the EXCEL trial (10) showed that the risk of mortality after CABG and PCI was different according to follow-up duration and might show a benefit for CABG with longer follow-up.

The main strength of this study is that we were able to identify clinically relevant differences in all-cause mortality between CABG and PCI because of collaboration with the principal investigators of 11 high-quality randomised trials. This collaboration allowed data to be pooled to provide sufficient power to examine an outcome that occurs reasonably infrequently. Indeed, all-cause mortality is considered to be the most clinically important and least biased endpoint, which is another strength of this analysis. Access to individual patient data facilitated analysis of outcomes in important subgroups and construction of Kaplan-Meier curves so that temporal associations between the interventions and mortality could be examined.

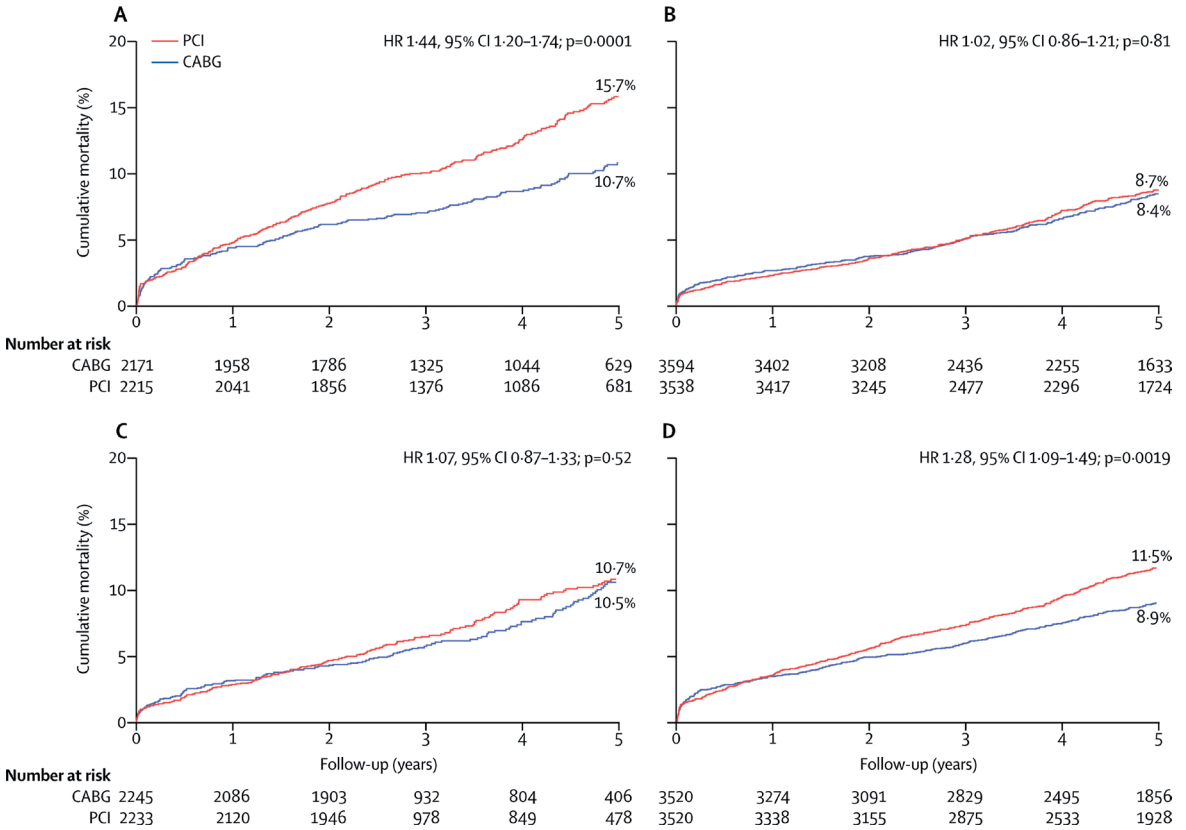


Figure 3. Mortality after CABG versus after PCI during 5 years' follow-up of patients with (A) or without (B) diabetes and with left main disease (C) or multivessel disease (D). Kaplan-Meier estimates are from the overall pooled patient population. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HR, hazard ratio.

Nevertheless, this study has several limitations. First, all the included trials assumed clinical equipoise between CABG and PCI. These trials had specific inclusion and exclusion criteria, and many patients were excluded because CABG or PCI was thought to be the preferred revascularisation strategy based on the age, risk profile, or coronary complexity of the individual (19). These criteria and the selection of patients resulted in only 22.1% of patients having a SYNTAX score of 33 or higher. Second, the inclusion and exclusion criteria led to significant heterogeneity in the baseline characteristics of patients from different trials, as shown by our assessment of frailty. Third, besides mortality, other outcomes that affect morbidity and quality of life, such as myocardial infarction, stroke, and repeat revascularisation, are important for the patient and should be considered by heart teams when deciding on the best revascularisation option for each patient. In an era of exponentially growing health-care costs, with a need to reduce expenses, the cost-effectiveness of PCI and CABG should also be evaluated. Fourth, the mean patient age was about 64 years, and the mean follow-up was 3.8 years. In view of the reasonably long life expectancy of patients with coronary artery disease, this follow-up is still too short to establish the full effect of the revascularisation method on survival, particularly considering the diverging or converging Kaplan-Meier curves in specific subgroups. Fifth, definitions and reporting of patient characteristics might have slightly differed between trials, which could have affected the results of the subgroup analyses and meant that we were unable to do a subgroup analysis according to renal function. Sixth, we could not include data from the LE MANS trial (14), although it is very unlikely that inclusion of these 105 patients with left main disease would have substantially altered the results, and thus the outcomes of this study are robust with respect to the available evidence.

CONCLUSION

In conclusion, we showed that 5 year mortality was significantly lower after CABG than after PCI. In particular, the benefit of CABG over PCI was shown in patients with multivessel disease and diabetes, but not in patients with multivessel disease without diabetes. Nor was there a benefit for CABG or PCI in patients with left main disease. Consideration of coronary lesion complexity is important when choosing the appropriate revascularisation strategy. Longer follow-up is needed to better define mortality differences between the interventions.

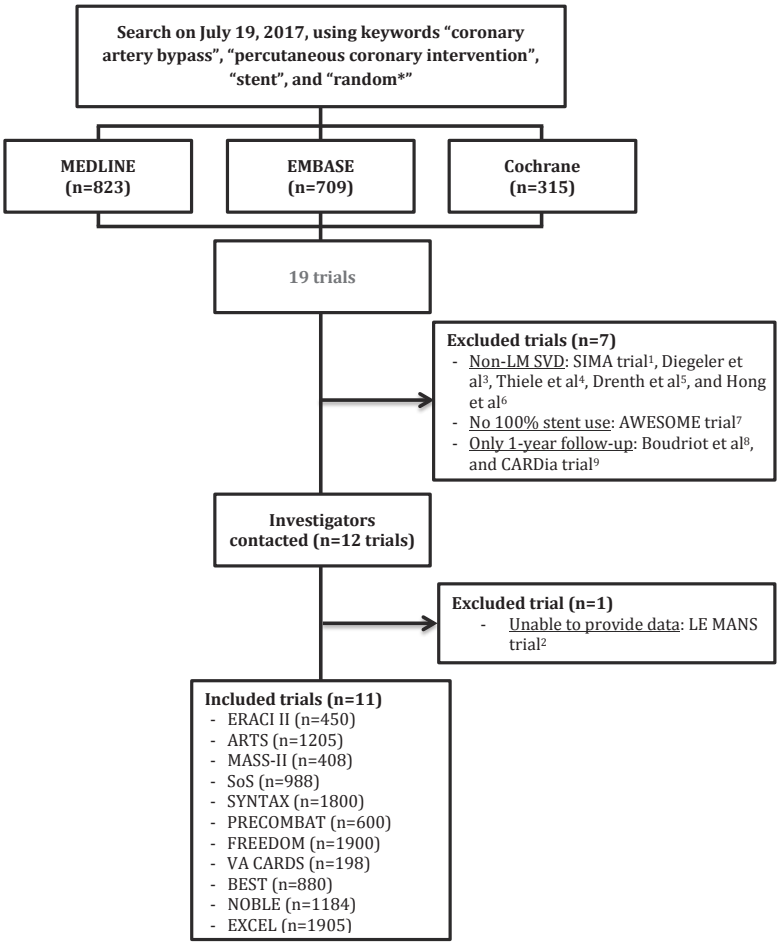
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SUPPLEMENTAL MATERIAL

APPENDIX 1. STUDY SELECTION FLOW-CHART.



APPENDIX 2. BASELINE AND PROCEDURAL CHARACTERISTICS IN INDIVIDUAL TRIALS.

Characteristic	ERACI II (n=450)	ARTS (n=1205)	MASS-II (n=408)	SoS (n=988)	SYNTAX (n=1800)	PRECOMB AT (n=600)	FREEDOM (n=1900)	VA CARDS (n=198)	BEST (n=880)	NOBLE (n=1184)	EXCEL (n=1905)
Patient inclusion	1996-1998	1997-1998	1995-2000	1996-1999	2005-2007	2004-2009	2005-2010	2006-2010	2008-2013	2008-2015	2010-2014
Study location	Argentina	Europe, South America, Australasia	Brazil	Europe, Canada	Europe, US	Korea	North America, South America, Europe, India, Australasia	US	Asia	Europe	North America, South America, Europe, India, Australasia
Heart team composition	"Clinical cardiologist, interventionalist, cardiac surgeon"	"Interventional cardiologist and cardiac surgeon"	"Interventionalist and surgeon"	"Interventionalist and surgeon"	"Interventional cardiologist and cardiac surgeon"	"Physicians and surgeons"	Not explicitly reported	"Interventional cardiologist and cardiothoracic surgeon"	"Physicians and surgeons"	"Interventional cardiologist and cardiac surgeon"	"Interventional cardiologist and cardiac surgeon"
Age	60·7 ± 10·2	60·6 ± 10·8	59·8 ± 9·0	61·4 ± 9·3	65·1 ± 9·7	62·2 ± 9·7	62·1 ± 9·1	62·4 ± 7·2	64·5 ± 9·4	66·2 ± 9·7	65·9 ± 9·6
Female sex	21% (93/450)	23% (283/1205)	31% (125/408)	21% (206/988)	22% (402/1800)	24% (141/600)	29% (544/1900)	1% (2/198)	29% (251/880)	22% (256/1184)	23% (441/1905)
BMI >30 kg/m^2	NA	22% (260/1203)	25% (100/408)	22% (220/982)	32% (579/1799)	3% (20/595)	42% (789/1896)	68% (132/195)	4% (35/880)	29% (336/1155)	34% (639/1904)
Smoking current	52% (233/540)	27% (323/1203)	33% (134/408)	15% (149/988)	21% (363/1760)	29% (172/600)	16% (298/1900)	25% (48/195)	20% (177/880)	20% (235/1170)	22% (415/1850)
Diabetes	17% (78/450)	17% (208/1205)	28% (115/408)	14% (142/988)	25% (452/1800)	32% (192/600)	100% (1900/1900)	100% (198/198)	41% (363/880)	15% (184/1184)	29% (554/1905)
Insulin treated	NA	NA	5% (20/408)	3% (28/988)	10% (182/1800)	3% (19/600)	32% (615/1900)	NA	4% (38/880)	NA	8% (147/1905)
Hypertension	71% (318/450)	45% (540/1205)	62% (253/408)	45% (447/988)	75% (1349/1787)	53% (317/600)	85% (1612/1900)	96% (187/195)	67% (591/880)	66% (775/1182)	74% (1404/1892)
Hypercholesterolemia	61% (275/450)	58% (694/1201)	73% (298/408)	52% (509/988)	78% (1391/1785)	41% (247/600)	84% (1592/1900)	58% (111/191)	52% (461/880)	80% (946/1183)	70% (1320/1875)
Peripheral vascular disease	23% (103/450)	5% (64/1205)	0% (0/408)	7% (66/988)	10% (177/1800)	4% (22/600)	10% (197/1900)	14% (27/195)	3% (27/880)	NA	9% (181/1896)
Carotid artery disease	6% (25/450)	NA	NA	NA	8% (148/1800)	NA	NA	NA	NA	NA	8% (156/1896)
Previous TIA/stroke	2% (10/450)	NA	NA	4% (37/988)	8% (150/1788)	NA	3% (65/1900)	10% (20/198)	8% (70/879)	NA	6% (119/1903)

Previous MI	28% (126/450)	43% (520/1205)	47% (191/408)	45% (448/988)	33% (585/1780)	6% (33/567)	26% (487/1900)	42% (81/195)	6% (54/880)	NA	17% (330/1888)
Moderate VEF (30-49%)	20% (88/446)	17% (189/1121)	4% (16/408)	19% (149/771)	17% (313/1800)	5% (26/542)	17% (329/1900)	29% (51/177)†	12% (90/744)	12% (120/1020)	12% (215/1804)
Poor LVEF (<30%)	0% (0/446)	0% (0/1121)	0% (0/408)	1% (4/771)	2% (34/1800)	1% (5/542)	1% (27/1900)	7% (12/177)	1% (5/744)	1% (5/1020)	1% (11/1804)
Unstable angina pectoris	92% (412/450)	36% (438/1205)	0% (0/408)	0% (0/988)	29% (513/1800)	45% (272/600)	31% (584/1900)	NA	44% (384/880)	17% (206/1183)	39% (744/1892)
Number of lesions	2·6 ± 0·6	2·8 ± 1·0	2·8 ± 0·8	2·8 ± 1·1	4·0 ± 1·7	3·0 ± 1·0	NA	3·6 ± 1·5	3·4 ± 1·2	1·7 ± 1·0	NA
Three-vessel disease	49% (220/450)	33% (403/1205)	58% (238/408)	42% (419/988)	61% (1095/1800)	51% (308/600)	83.4% (1573/1887)	66% (120/181)	77% (679/880)	NA	NA
Left main disease	5% (21/450)	0.1% (1/1205)	0% (0/408)	1% (7/988)	39% (705/1800)	100% (600/600)	0.4% (8/1900)	0% (0/198)	5% (47/880)	100% (1184/1184)	100% (1905/1905)
SYNTAX score	NA	NA	NA	NA	28·7 ± 11·4	25·1 ± 10·0	26·2 ± 8·6	NA	24·8 ± 7·7	22·4 ± 7·3	26·5 ± 9·3
PCI – DES used	0% (0/222)	0% (0/593)	0% (0/205)	0% (0/488)	100% (885/885)	100% (276/276)	100% (939/939)	99% (92/93)	100% (413/413)	100% (580/580)	100% (935/935)
DES type	-	-	-	-	Paclitaxel	Sirolimus	Paclitaxel and Sirolimus	Mixed paclitaxel, sirolimus, everolimus, zotarolimus	Everolimus	Majority Biolimus	Everolimus
PCI – number of stents	1.4 ± 0.6	NA	1.2 ± 0.9	2.6 ± 1.4	4.6 ± 2.3	2.7 ± 1.4	4.1 ± 1.9	NA	3.4 ± 1.4	2.2 ± 1.2	2.4 ± 1.5
CABG – LIMA use	95% (198/209)	NA	95% (188/198)	93% (450/485)	97% (827/854)	94% (233/248)	94% (843/893)	NA	100% (382/382)	96% (545/565)	99% (908/923)
CABG – BIMA use	0.5% (1/209)	NA	32% (65/203)	10% (50/485)	28% (236/854)	NA	12% (110/893)	NA	NA	8% (44/549)	29% (265/923)
CABG – off-pump	NA	NA	NA	NA	15% (128/854)	63% (155/248)	18% (165/893)	32% (26/82)	66% (252/382)	16% (88/564)	29% (271/923)
Complete revascularization	68% (303/448)	82% (992/1205)	57% (224/408)	70% (693/988)	60% (1043/1741)	69% (416/600)	90% (1701/1900)	NA	61% (518/855)	94% (543/577)*	NA
Aspirin at discharge	100% (450/450)	NA	98% (391/397)	NA	92% (1633/1766)	99% (593/600)	98% (1826/1867)	98% (172/176)	97% (852/880)	93% (539/580)*	98% (1823/1867)

Thienopyridine at discharge	53% (238/450)	NA	48% (194/408)	NA	59% (1037/1766)	94% (565/600)	62% (1158/1867)	55% (96/176)	93% (818/880)	97% (566/580)*	66% (1227/1867)
DAPT at discharge	53% (238/450)	NA	47% (187/397)	NA	56% (987/1766)	93% (560/600)	81% (1513/1867)	54% (94/176)	92% (806/880)	92% (532/580)*	65% (1204/1867)
Statin at discharge	NA	NA	NA	NA	80% (1425/1766)	73% (431/592)	88% (1566/1770)	NA	83% (733/880)	NA	95% (1740/1840)
Beta-blocker at discharge	NA	NA	NA	NA	80% (1412/1766)	51% (303/592)	83% (1477/1770)	NA	56% (489/880)	NA	89% (1617/1812)
ACEI or ARB at discharge	NA	NA	NA	NA	59% (1042/1766)	33% (198/592)	75% (1334/1770)	NA	35% (307/880)	NA	50% (912/1839)
Calcium-channel blocker at discharge	NA	NA	NA	NA	22% (391/1766)	54% (320/592)	23% (405/1770)	NA	52% (459/880)	NA	7% (120/1838)
Mean follow-up (years)	4·7 ± 1·1	4·8 ± 0·9	4·5 ± 1·3	4·7 ± 0·9	4·4 ± 1·4	4·7 ± 1·0	3·5 ± 1·4	1·4 ± 0·9	4·0 ± 1·3	3·2 ± 1·5	2·6 ± 0·7

*Data are available only for the PCI group.

†In the VA CARDS trial, the cut-off for a moderate LVEF was 35-55%.

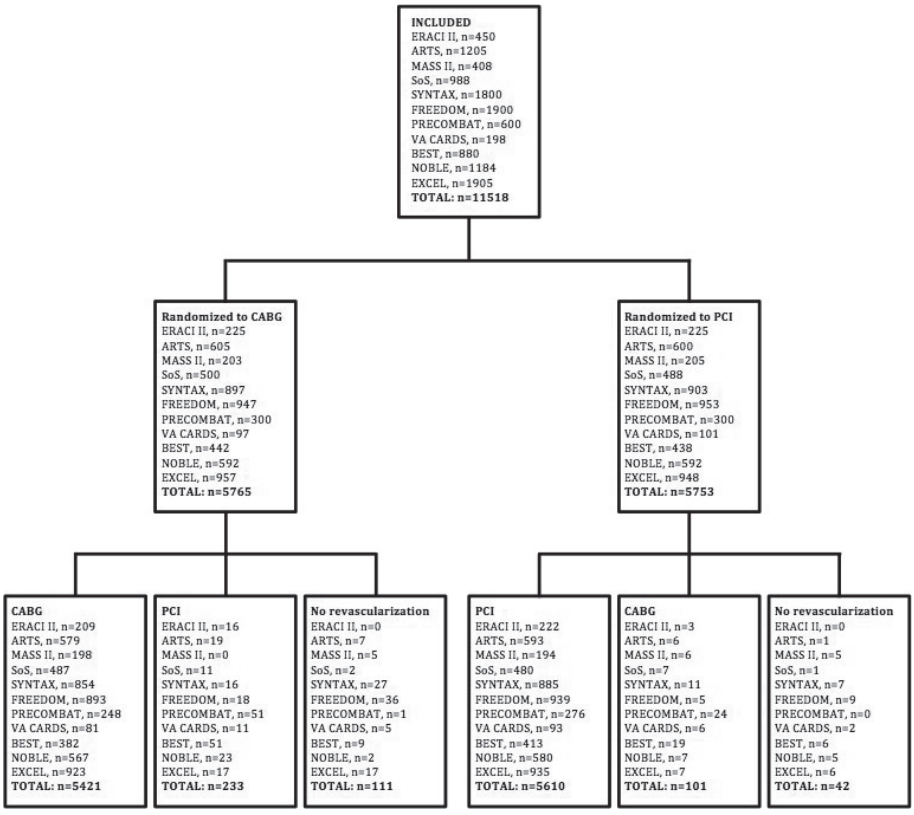
Values are present as mean ± SD or n/N (%). NA, not available; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug-eluting stents; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; DAPT, dual antiplatelettherapy.

APPENDIX 3. ASSESSMENT OF RISK OF BIAS IN INDIVIDUAL TRIALS.

Trial	Random sequence generation	Allocation concealment	Blinding patients and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other Bias
ERACI II	+	-	-	+	+	+	+
ARTS	?	-	-	+	+	+	+
MASS-II	?	-	-	+	+	+	+
SoS	+	-	-	+	+	+	+
SYNTAX	+	-	-	+	-	+	+
PRECOMBAT	+	-	-	+	+	+	-
FREEDOM	+	-	-	+	+	+	+
VA CARDS	+	-	-	+	+	+	-
BEST	+	-	-	+	+	+	-
NOBLE	+	-	-	+	+	+	+
EXCEL	+	-	-	+	+	+	+

The assessment of "Random sequence generation" was rated "?" for the ARTS and MASS-II trials because it was not specified exactly how randomization took place. The assessment of "Allocation concealment" was rated standard as "-" for all trials because patients had to be informed on the allocated procedure, since these trials evaluate interventional procedures. The assessment of "Blinding of patients and personnel" was rated standard as "-" for all trials because the two interventional procedures evaluated are inherently different and patients cannot be blinded. The assessment of "Blinding of outcome assessment" was rated standard as "+" for all trials as no bias can be introduced for the endpoint of all-cause mortality, and thus blinding is irrelevant; yet still a clinical events committee reviewed all events. The assessment of "Incomplete outcome data" was "-" for the SYNTAX trial because >10% of patients after CABG were lost to follow-up, while this rate was only 3.5% after PCI. The assessment of "Selective reporting" was rated "+" for all trials because all trials reported all-cause mortality. The assessment of "Other bias" was rated as "-" in the PRECOMBAT, VA-CARDS, and BEST trials because a relatively high percentage (>10%) of patients did not receive the allocated treatment because of cross over or no interventional treatment.

APPENDIX 4. INFORMATION ON RANDOMIZATION AND ACTUAL TREATMENTS PERFORMED.



APPENDIX 5. TIME-DEPENDENT MODELS OF PCI VERSUS CABG.

Patient group	Time interval	First hazard		Second hazard		Frailty term (γ)	P for heterogeneity
		HR (95% CI)	Time interval	HR (95% CI)			
Overall	All	0-365 days	0·97 (0·80- 1·19)	365-1825 days	1·38 (1·17- 1·62)	0·39	<0·0001
	Diabetes	0-280 days	1·05 (0·78- 1·42)	280-1825 days	1·76 (1·38- 2·24)	0·11	<0·0001
	No diabetes	0-280 days	0·84 (0·62-1·15)	280-1825 days	1·12 (0·90-1·37)	0·0880	<0·0001
	SYNTAX score 0-22	0-470 days	0·63 (0·41-0·99)	470-1825 days	1·40 (0·97-2·01)	0·0454	0·0094
	SYNTAX score 23-32	0-470 days	1·03 (0·72-1·46)	280-1825 days	1·36 (0·99-1.87)	0·0657	0·0031
	SYNTAX score ≥33	0-470 days	1·83 (1·18-2·82)	280-1825 days	1·34 (0·93-1·95)	0·0191	0·0602
	Bare-metal stent	0-730 days	0·90 (0·64-1·27)	730-1825 days	1·22 (0·86-1·73)	0·16	<0·0001
	Drug-eluting stent	0-500 days	1·08 (0·87-1·34)	500-1825 days	1·45 (1·18-1·77)	0·36	<0·0001
	First- generation drug-eluting stent	0-730 days	1·12 (0·87-1·45)	730-1825 days	1·31 (1·01-1·73)	0·23	<0·0001
	Newer- generation drug-eluting stent	0-180 days	0·68 (0·43-1·10)	180-1825 days	1·65 (1·21-2·25)	0·13	0·0020
MVD	All	0-280 days	0·99 (0·76-1·29)	280-1825 days	1·46 (1·20-1·77)	0·40	<0·0001
	Diabetes	0-280 days	1·11 (0·78-1·58)	280-1825 days	1·77 (1·34-2·34)	0·16	<0·0001
	No diabetes	0-370 days	0·94 (0·64-1·40)	370-1825 days	1·16 (0·88-1·53)	0·090	<0·0001
	SYNTAX score 0-22	0-600 days	0·65 (0·37-1·14)	600-1825 days	1·78 (1·05-3·01)	0·0935	0·0140
	SYNTAX score 23-32	0-600 days	1·43 (0·91-2·24)	600-1825 days	1·60 (1·00-2·55)	0·0720	0·0065
	SYNTAX score ≥33	0-600 days	1·72 (0·97-3·04)	600-1825 days	1·70 (0·95-3·01)	0·0252	0·0505
LM	All	0-730 days	1·09 (0·82-1·44)	730-1825 days	1·06 (0·76-1·48)	0·0845	<0·0001
	Diabetes	0-730 days	1·22 (0·79-1·86)	730-1825 days	1·70 (0·86-3·35)	0·0543	0·0172
	No diabetes	0-730 days	0·98 (0·67-1·43)	730-1825 days	0·90 (0·61-1·32)	0·0604	0·0027
	SYNTAX score 0-22	0-570 days	0·68 (0·37-1·25)	570-1825 days	1·12 (0·64-1·94)	<0·0001	0·0001
	SYNTAX score 23-32	0-570 days	0·79 (0·50-1·25)	570-1825 days	1·13 (0·70-1·90)	0·0626	0·0093
	SYNTAX score ≥33	0-570 days	1·70 (0·96-3·02)	570-1825 days	1·16 (0·67-1·99)	0·0222	0·0647
DM	SYNTAX score 0-22	0-730 days	0·60 (0·36-0·99)	730-1825 days	2·70 (1·40-5·21)	<0·0001	0·0001
	SYNTAX score 23-32	0-730 days	1·30 (0·90-1·89)	730-1825 days	1·35 (0·78-2·34)	0·0159	0·0713
	SYNTAX score ≥33	0-730 days	1·78 (1·06-2·97)	730-1825 days	1·75 (0·92-3·34)	<0·0001	0·0001
NO DM	SYNTAX score 0-22	0-730 days	0·91 (0·52-1·59)	730-1825 days	0·99 (0·55- 1·79)	<0·0001	0·0193
	SYNTAX score 23-32	0-730 days	0·90 (0·54-1·48)	730-1825 days	1·19 (0·70-2·03)	0·0807	0·0096
	SYNTAX score ≥33	0-730 days	1·80 (1·00-3·23)	730-1825 days	1·00 (0·58-1·73)	0·0089	0·0884

Results of time-dependent models provide a hazard ratio for a first time interval and a second interval with the duration of this interval being dependent on when the hazard changes, which can be different according to the patient cohort, depending on the visual inspection of the Schoenfeld residuals for that particular analysis. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

APPENDIX 6. FIVE-YEAR OUTCOMES WITHIN GROUPS WITH AND WITHOUT DIABETES ACCORDING TO SYNTAX SCORE TERTILES.

	Diabetes				No diabetes			
	PCI (n=1819)	CABG (n=1782)	HR (95% CI) P-value	P for interaction	PCI (n=2262)	CABG (n=2275)	HR (95% CI) P-value	P for interaction
SYNTAX score 0-22	13·0% (58/622)	9·8% (53/655)	1·09 (0·75-1·58) P=0·66	Pint=0·25	6·6% (47/911)	7·0% (47/930)	0·95 (0·63-1·42) P=0·80	P_{int}=0·66
SYNTAX score 23-32	15·1% (101/814)	12·5% (67/723)	1·32 (0·97-1·79) P=0·0817		9·9% (62/863)	9·4% (55/822)	1·03 (0·71-1·48) P=0·88	
SYNTAX score ≥33	20·0% (63/383)	12·3% (38/404)	1·77 (1·18-2·64) P=0·0056		13·6% (54/488)	11·1% (45/523)	1·32 (0·89-1·96) P=0·16	

Kaplan-Meier estimates are from the overall pooled patient population. Hazard ratios (HRs) with confidence intervals (CIs) are derived from Cox proportional hazards random-effects models stratified by trial.

APPENDIX 7 SUPPLEMENTARY REFERENCES IN THE APPENDIX.

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Chapter 7

Causes of Death Following PCI Versus CABG in Complex CAD: 5-Year Follow-Up of SYNTAX

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ABSTRACT

BACKGROUND: There are no data available on specific causes of death from randomized trials that have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI).

OBJECTIVES: The purpose of this study was to investigate specific causes of death, and its predictors, after revascularization for complex coronary disease in patients.

METHODS: An independent Clinical Events Committeeconsisting of expert physicians who were blinded tothe study treatment subclassified causes of death as cardiovascular (cardiac and vascular), noncardiovascular, or undetermined according to the trial protocol. Cardiac deaths were classified as sudden cardiac, related to myocardial infarction (MI), and other cardiac deaths.

RESULTS: In the randomized cohort, there were 97 deaths after CABG and 123 deaths after PCI during a 5-year follow-up. After CABG, 49.4% of deaths were cardiovascular, with the greatest cause being heart failure, arrhythmia, or other causes (24.6%), whereas after PCI, the majority of deaths were cardiovascular (67.5%) and as a result of MI (29.3%). The cumulative incidence rates of all-cause death were not significantly different between CABG and PCI (11.4% vs. 13.9%, respectively; p = 0.10), whereas there were significant differences in terms of cardiovascular (5.8% vs. 9.6%, respectively; p = 0.008) and cardiac death (5.3% vs. 9.0%, respectively; p = 0.003), which were caused primarily by a reduction in MI-related death with CABG compared with PCI (0.4% vs. 4.1%, respectively; p <0.0001). Treatment with PCI versus CABG was an independent predictor of cardiac death (hazard ratio: 1.55; 95% confidence interval: 1.09 to 2.33; p = 0.045). The difference in MI-related death was seen largely in patients with diabetes, 3-vessel disease, or high SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial scores.

CONCLUSIONS: During a 5-year follow-up, CABG in comparison with PCI was associated with a significantly reduced rate of MI-related death, which was the leading cause of death after PCI. Treatments following PCI should target reducing post-revascularization spontaneous MI. Furthermore, secondary preventive medication remains essential in reducing events post-revascularization.

INTRODUCTION

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are both used for myocardial revascularizaˆtion in patients with complex coronary artery disease (CAD) with an indication for revascularization (1). A large number of studies have reported or compared outcomes of CABG and PCI as optimum treatment strategies (2), but data are limited on the causes, circumstances, and the mechanisms of death after these procedures.

Observational studies have reported causes of death after PCI and CABG (3–5), but these results are difficult to interpret because the cause of death may not always be clear in retrospect. Therefore, data from randomized trials in which a Clinical Events Committee (CEC) adjudicates deaths provide more valuable information. Two randomized clinical trials that compared CABG with medical therapy have shown that CABG was particularly effective in reducing rates of sudden cardiac death (5,6), but no comparisons between PCI and CABG on the specific causes of death are available from randomized trials.

Assessment of the cause of death in contemporary practice should help to target potential underlying mechanisms of death and further develop effective interventions to improve survival after myocardial revascularization. The goal of the present study was to investigate the specific cause of death, and its predictors, in patients enrolled in the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial, which represents a contemporary cohort of patients who underwent CABG or received drugeluting stents (DES).

METHODS

Study design, patients, and randomization

The design, methods, and procedural details of the SYNTAX trial have been reported previously (7–9). The SYNTAX study was a prospective, multinational, randomized trial conducted in 85 centers in the United States and Europe. In this study, 1,800 patients with de novo left main (LM) or 3-vessel disease (3VD) were randomly assigned to undergo CABG or PCI with first-generation paclitaxel-eluting stents (Taxus Express, Boston Scientific, Natick, Massachusetts). Based on clinical judgment and consensus of a heart team that consisted of a cardiac surgeon and interventional cardiologist at each center, patients with anticipated

clinical equipoise through CABG and PCI were randomized (CABG, n = 897 and PCI, n = 903).

Randomization occurred via a central interactive voice response system in random block sizes per site based on the presence or absence of LM disease and medically treated diabetes mellitus. Patients suitable for PCI only entered the PCI registry (CABG ineligible patients, n = 198), whereas those suitable for CABG only entered the CABG registry (PCI ineligible patients, n = 1,077) (10). Within the nested registries, all PCI patients and 649 randomly allocated CABG patients underwent 5-year follow-up. Routine follow-up assessments were performed by clinical visits or telephone interviews at 1, 6, and 12 months, and annually thereafter. All the clinical endpoints were assessed by the event-adjudication CEC. Data collection and quality were monitored systematically by the principal investigators and safety monitoring committee. Complete 5-year follow-up (clinical follow-up or death) after randomization to CABG and PCI was achieved in 805 (89.7%) and 871 (96.5%) patients, respectively. Follow-up was complete for 184 patients (95.8%) in the PCI registry and for 607 patients (94.3%) in the CABG registry.

The post-procedure medication regimens and the use of secondary-prevention therapy according to American College of Cardiology and American Heart Association treatment guidelines (11,12) was strongly recommended for all patients. Medication use for the randomized cohort was collected at baseline, discharge, at 1 and 6 months, and at 1, 3, and 5 years post-allocation. For the nested registries, this was collected at baseline and discharge.

This study was done in accordance with the principles of the Declaration of Helsinki, and all sitespecific institutional review boards and applicable regulatory agencies approved the study protocol before study initiation.

DEFINITIONS. The definitions used for the classifications of adverse events have been previously reported elsewhere (9). Mortality data during the course of follow-up were collected prospectively. Collection started directly after randomization to finalizing the 5-year follow-up; therefore, this included post-randomization pre-procedural deaths, operative deaths, and deaths during follow-up. For each death event, standardized electronic case report forms were used by local principal investigators to categorize a terminal event in detail. The case report form included a structured narrative description of date and location of death, onset of adverse events that preceded the fatal outcome, circumstances of death, and description of treatments, if initiated. For all deaths, all available information was obtained and

forwarded to the independent CEC, including the death certificates, the coroner's report, and other records (hospital discharge summary, pathology, laboratory, radiology, and other diagnostic data). The CEC was composed of physicians who were experts in cardiology, cardiac surgery, and neurology. Two CEC members reviewed all deaths independently in a blinded manner. Disagreements between reviewers and principal investigators were discussed and resolved by full CEC consensus.

Because the SYNTAX study began before publication of the Academic Research Consortium definition (13), it used specially designed definitions of death. The CEC classified deaths into cardiovascular or noncardiovascular, according to the trial protocol. Cardiovascular deaths were further classified as cardiac (sudden cardiac deaths, myocardial infarction (MI), progressive heart failure, and arrhythmia) and cardiac others (which included other cardiac causes, e.g., cardiac tamponade and cardiac deaths with insufficient information for definitive classification), vascular (stroke, aortic dissection, and pulmonary embolism), and vascular others (major hemorrhage, peripheral embolism, and other). Using these classifications, the following cardiac subgroups were defined and analyzed: 1) sudden cardiac deaths; 2) MI-related deaths; and 3) congestive heart failure (CHF), arrhythmia, and all other cardiac deaths, the latter of which were combined together into a single subgroup because of the low number of cases in each particular subgroup. Noncardiovascular deaths included those resulting from chronic respiratory disease, pneumonia, malignancy, diabetes mellitus, and other conditions (which included infections, accidents, suicides, trauma-related, chronic disease, and others). When a specific cause of death could not be determined from the available evidence, the death was classified as undetermined. Every death was attributed to one of the specific causes exclusively.

Major adverse events were considered nonfatal if no death occurred within 30 days of the event, and when it was not possible to establish any association between the event and death from the narrative description of death.

During the Heart Team meeting, both the interventional cardiologist and surgeon documented which vessels that were >1.5 mm diameter and >50% stenosis needed revascularization. In the original trial protocol, incomplete revascularization was defined when the actual revascularization did not correlate with this pre-operative Heart Team statement.

STATISTICAL ANALYSES. All analyses in the randomized cohort were done according to the intention-to-treat principle, whereas in the nested registries,

outcomes were presented according to the as-treated principle. As previously described, no statistical comparisons between the PCI and CABG registries were performed (10).

Continuous variables were reported as mean ± SD and compared with the Student *t* test. Binary variables were expressed as counts and/or percentages and compared with the chi-square test or Fisher exact test, as appropriate. Five-year rates of death were estimated using the Kaplan-Meier method, and comparisons between PCI and CABG were done using the log-rank test. For the randomized cohort, subgroup analyses were performed for pre-specified groups of patients with LM or 3VD and diabetic patients or nondiabetic patients, and post-hoc groups according to SYNTAX score tertiles (low 0 to 22, intermediate 23 to 32, and high >=33) and completeness of revascularization. The p values for interaction were performed using chi-square tests. Cox proportional hazard models for specific causes of death during the 5-year follow-up were constructed to provide hazard ratios (HRs) associated with PCI versus CABG treatment. The proportional hazards assumption of the Cox models was evaluated with Schoenfeld residuals (14). There was no evidence of departure from the assumption of proportionality. Multivariate analyses were performed using Cox proportional hazard models with backward selection of variables to construct a set of independent predictors. Variables considered of clinical importance and with a p value <0.15 in univariate analysis were considered in the multivariate models (Supplemental Appendix). Models were constructed for the overall randomized cohort and CABG and PCI randomized groups separately, as well as for the PCI and CABG registry patients separately. The performance of the models was tested using receiver-operating characteristics curves. A 2-sided p value of <0.05 was considered to be statistically significant for all tests. Analyses were performed using SPSS version 20.0 statistical software (IBM, Armonk, New York).

RESULTS

CAUSES OF DEATH. During the 5-year follow-up, there were 123 deaths after PCI and 97 deaths after CABG in the randomized cohort. Among PCI patients, the majority of deaths were cardiovascular (67.5%, n = 83), of which nearly all deaths were from cardiac causes (Table 1). The largest cause of cardiovascular death after PCI was related to MI (Figure 1A). In the CABG group, cardiovascular deaths accounted for 49.4% (n = 48), noncardiovascular deaths for 48.5% (n = 47), and 2.1% (n = 2) of deaths occurred due to undetermined causes (Table 1). Of

cardiovascular death, only a few deaths were from vascular causes. The greatest cause of cardiovascular death after CABG was CHF, arrhythmia, or other causes (Figure 1A).

In the PCI registry, 22 (38.6%) patients died of cardiovascular causes, and the majority of deaths (50.9%, n = 33) were due to noncardiovascular causes (Figure 1B). Within the CABG registry, cardiovascular deaths represented 36.7% (n = 29) of deaths, whereas noncardiovascular deaths occurred in 41.8% (n = 33) of cases. Of note, noncardiovascular deaths were most often caused by malignancies. Rates of all-cause death at 5-year follow-up were 30.0% (n = 57) in the PCI registry and 12.6% (n = 79) in the CABG registry (Table 1). Specific causes of death are shown in Figure 3.

Table 1. Specific Causes of Death in the SYNTAX Trial.

Causes of Death	PCI	CABG	HR (95% CI)	p Value	PCI Registry	CABG Registry
Total	123 (13.9)	97 (11.4)	1.23 (0.94–1.60)	0.10	57 (30.0)	79 (12.6)
Cardiovascular death	83 (9.6)	48 (5.8)	1.62 (1.13–2.31)	0.008	22 (12.1)	29 (4.7)
Cardiac	78 (9.0)	43 (5.3)	1.70 (1.17–2.47)	0.003	17 (9.5)	22 (3.6)
Sudden cardiac death	24 (2.8)	15 (1.9)	1.61 (0.83–3.11)	0.16	5 (2.7)	6 (1.0)
Myocardial infarction	36 (4.1)	4 (0.4)	8.43 (2.99–23.67)	<0.0001	3 (1.8)	2 (0.3)
Heart failure	7 (0.8)	13 (1.6)	0.50 (0.20–1.26)	0.14	5 (2.7)	6 (1.0)
Arrhythmia	1 (0.1)	1 (0.1)	0.95 (0.06–15.14)	0.97	0	1 (0.2)
Other	10 (1.1)	11 (1.4)	0.85 (0.36–2.01)	0.71	4 (2.2)	6 (1.0)
CHF/cardiac other	18 (2.1)	24 (3.0)	0.67 (0.37–1.24)	0.20	9 (4.8)	14 (2.2)
Vascular	5 (0.6)	5 (0.5)	0.93 (0.27–3.23)	0.91	5 (2.7)	7 (1.1)
CVA	3 (0.3)	3 (0.3)	0.94 (0.19–4.64)	0.94	1 (0.5)	3 (0.5)
Aortic dissection	0	0	–	>0.99	0	2 (0.3)
Pulmonary embolism	0	1 (0.1)	0.014 (0–138,818)	0.60	2 (1.1)	0
Other	2 (0.2)	1 (0.1)	1.86 (0.17–20.55)	0.61	2 (1.1)	2 (0.3)
Noncardiovascular death	40 (4.3)	47 (5.6)	0.85 (0.55–1.31)	0.46	29 (14.9)	33 (5.3)
Chronic respiratory disease	0	1 (0.1)	0.015 (0–141,247)	0.61	3 (1.8)	1 (0.2)
Pneumonia	4 (0.4)	3 (0.3)	1.88 (0.34–10.29)	0.46	6 (3.1)	3 (0.5)
Cancer	20 (2.2)	20 (2.4)	1.04 (0.55–1.97)	0.90	8 (4.2)	20 (3.1)
DM	1 (0.1)	0	60.88 (0–595,324)	0.62	0	1 (0.2)
Other	15 (1.6)	23 (2.8)	0.61 (0.32–1.17)	0.14	12 (5.9)	8 (1.3)
Undetermined death	0	2 (0.2)	0.016 (0–1262)	0.47	6 (3.1)	17 (2.6)

Values are number of events (%), unless otherwise indicated.

CABG, coronary artery bypass grafting; CHF, congestive heart failure; CI, confidence interval; CVA, cerebral vascular accident; DM, diabetes mellitus; HR, hazard ratio; PCI, percutaneous coronary intervention; SYNTAX, TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries.

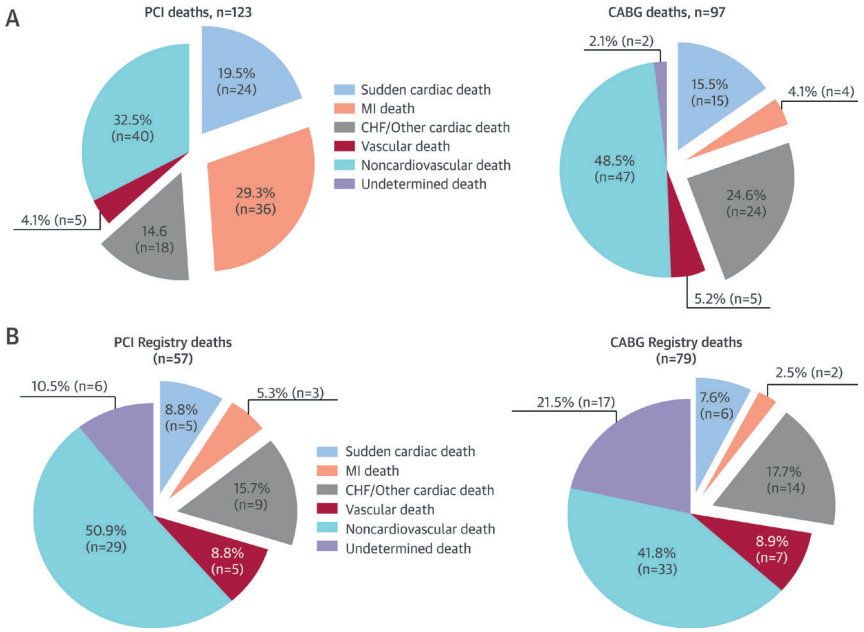


Figure 1. Causes of Death in the SYNTAX (A) Randomized Cohort and (B) Nested Registries
CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; Other Cardiac, arrhythmia and all other cardiac deaths; PCI, percutaneous coronary intervention; SYNTAX, TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries.

INCIDENCES OF DEATH. At 5-year follow-up, there was a significant difference in favor of CABG in terms of cardiovascular death ($p = 0.008$), but not of noncardiovascular death ($p = 0.46$) (Figure 2). The difference in cardiovascular death was the result of a significantly lower rate of death due to MI (CABG 0.4% vs. PCI 4.1%; $p < 0.0001$), whereas rates of sudden cardiac death or death by CHF or arrhythmia were similar. All-cause death rates were not significantly different ($p = 0.10$) (Figure 2).

SUBGROUP ANALYSES. Subgroup analyses revealed that the reduced rates of cardiac death after CABG in comparison with PCI were particularly evident in patients with diabetes, 3VD, and a high SYNTAX score, although none of the interaction tests were significant (Figure 4A). More in-depth subgroup analyses in rates of sudden cardiac deaths, MI-related deaths, and CHF and/or other cardiac deaths were performed to detect the cause of this difference (Figure 4B). Among all patient subgroups, the rate of sudden cardiac death was numerically higher after PCI than after CABG, although this failed to reach statistical significance. Only

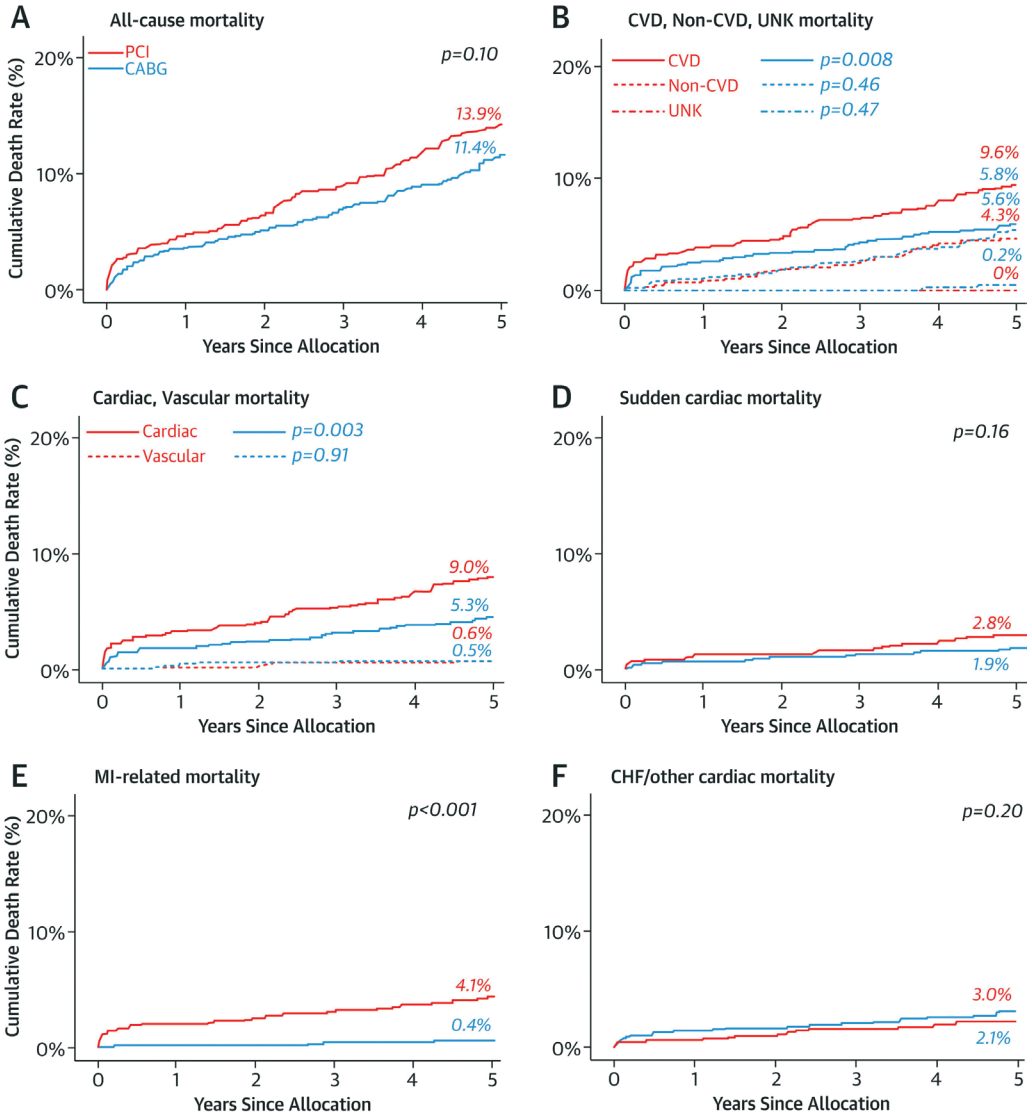


Figure 2. Kaplan-Meier Cumulative Event Curves by Specific Causes of Deaths in the SYNTAX Randomized Cohort. Analyses include Kaplan-Meier estimates of all-cause mortality **(A)**; a subdivision in cardiovascular, non-cardiovascular, and unknown cause of mortality **(B)**; subdividing cardiovascular mortality in cardiac and vascular mortality **(C)**; and cardiac death subdivided into individual components of sudden cardiac mortality **(D)**, MI-related mortality **(E)**, and CHF/other cardiac mortality **(F)**. CVD, cardiovascular; Non-CVD, noncardiovascular; UNK, unknown/undetermined; other abbreviations as in Figure 1.

patients with a high SYNTAX score had significantly higher rates of sudden cardiac death after PCI versus CABG (HR: 5.09; 95% confidence interval (CI): 1.46 to 17.71; p = 0.011). Differences in MI-related deaths were consistently in favor of CABG and were particularly prominent in patients with diabetes, 3VD, and higher SYNTAX scores. There were no differences between PCI and CABG in terms of deaths due to CHF or other cardiac causes, although patients with a lower SYNTAX score did appear to have a nonsignificant benefit with PCI (Figure 4B).

Incomplete revascularization with PCI was associated with risk of cardiac deaths (HR: 1.89; 95% CI: 1.20 to 2.98; p = 0.006), which was driven by deaths due t o CHF and/or other cardiac causes (HR: 5.97; 95% CI: 1.72 to 20.78; p = 0.005) (Figure 4C). In CABG patients, there was no increased risk in any specific causes of death associated with incomplete revascularization (Figure 4C).

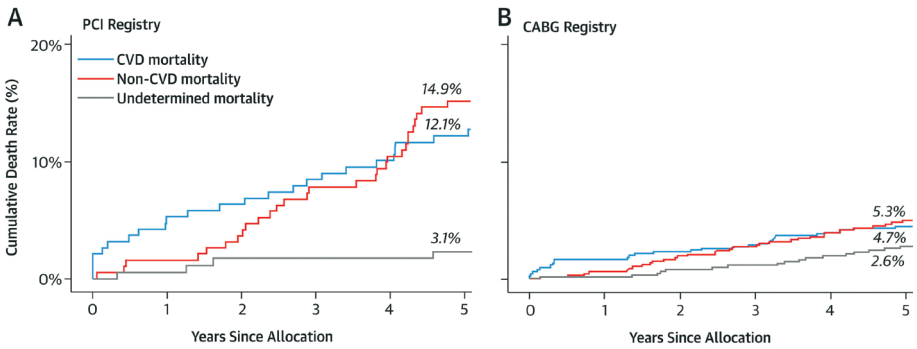
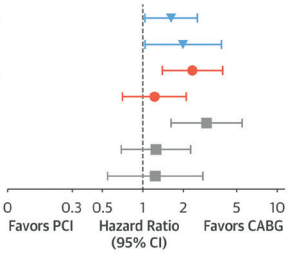


Figure 3. The Kaplan-Meier Cumulative Event Curves by Specific Causes of Deaths in the SYNTAX Nested Registries. The Kaplan-Meier cumulative event curves by specific causes of deaths in the SYNTAX PCI **(A)** and CABG **(B)** nested registries. Abbreviations as in Figures 1 and 2.

PATIENT CHARACTERISTICS AND PREDICTORS OF ALL-CAUSE AND CARDIAC DEATH. Randomized trial. Significant baseline and lesion characteristics of patients who were alive or dead at 5 years after revascularization are summarized in Table 2 (complete results are in the Supplemental Table 1). Patients who died after both PCI or CABG had a higher risk profile at baseline than those who were still alive; they were older, had a higher presence of co-morbidities (diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, carotid artery disease, and creatinine >200 mmol/l), which resulted in higher EuroSCORE values. Moreover, rates of medically treated diabetes and the mean SYNTAX score were significantly higher in patients who died after PCI, but these rates were not higher in patients who died after CABG.

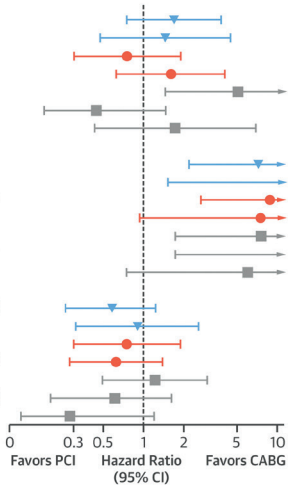
A

Cause of deaths	PCI	CABG	HR (95% CI)	*P*-value	Interaction *P*-value
Cardiac deaths					
Non-diabetic patients	50/672 (7.7%)	30/676 (4.9%)	1.62 (1.03-2.55)	0.035	0.30
Diabetic patients	28/231 (12.7%)	13/221 (6.5%)	2.01 (1.04-3.88)	0.034	
Three-vessel disease	48/546 (9.2%)	20/548 (4.0%)	2.34 (1.39-3.95)	<0.001	0.76
left main disease	30/357 (8.6%)	23/348 (7.2%)	1.23 (0.71-2.11)	0.46	
SYNTAX score≥33	38/290 (13.6%)	14/315 (4.9%)	2.99 (1.62-5.52)	<0.001	0.61
SYNTAX score 23-32	26/310 (8.8%)	19/300 (7.1%)	1.25 (0.69-2.26)	0.45	
SYNTAX score 0-22	14/299 (4.8%)	10/275 (3.8%)	1.24 (0.55-2.80)	0.60	



B

Cause of deaths	PCI	CABG	HR (95% CI)	*P*-value	Interaction *P*-value
Sudden cardiac deaths					
Non-diabetic patients	16/672 (2.5%)	9/676 (1.5%)	1.68 (0.74-3.81)	0.21	0.93
Diabetic patients	8/231 (3.6%)	6/221 (3.0%)	1.45 (0.47-4.43)	0.52	
Three-vessel disease	12/546 (2.3%)	8/548 (1.6%)	1.62 (0.64-4.11)	0.31	0.69
Left main disease	12/357 (3.5%)	7/348 (2.2%)	1.59 (0.62-4.03)	0.33	
SYNTAX score≥33	14/290 (5.0%)	3/315 (1.0%)	5.09 (1.46-17.71)	0.011	0.44
SYNTAX score 23-32	4/310 (1.3%)	8/300 (2.7%)	0.44 (0.13-1.46)	0.18	
SYNTAX score 0-22	6/299 (2.1%)	4/275 (1.4%)	1.72 (0.43-6.86)	0.44	
MI-related deaths					
Non-diabetic patients	23/672 (3.5%)	3/676 (0.5%)	7.26 (2.18-24.18)	0.001	0.096
Diabetic patients	13/231 (5.9%)	1/221 (0.5%)	11.66 (1.52-89.11)	0.018	
Three-vessel disease	28/546 (5.3%)	3/548 (0.6%)	8.78 (2.67-28.87)	<0.001	0.12
Left main disease	8/357 (2.3%)	1/348 (0.3%)	7.42 (0.93-59.36)	0.059	
SYNTAX score≥33	14/290 (5.0%)	2/315 (0.7%)	7.59 (1.72-33.40)	0.007	0.39
SYNTAX score 23-32	15/310 (5.0%)	1/300 (0.4%)	13.19 (1.74-99.87)	0.012	
SYNTAX score 0-22	7/299 (2.4%)	1/275 (0.4%)	6.02 (0.74-48.95)	0.093	
CHF/Other cardiac deaths					
Non-diabetic patients	11/672 (1.7%)	18/676 (2.9%)	0.58 (0.27-1.23)	0.15	0.49
Diabetic patients	7/231 (3.2%)	6/221 (3.1%)	0.90 (0.31-2.56)	0.84	
Three-vessel disease	8/546 (1.5%)	9/548 (1.9%)	0.75 (0.30-1.90)	0.55	0.22
Left main disease	10/357 (2.9%)	15/348 (4.7%)	0.62 (0.28-1.37)	0.24	
SYNTAX score≥33	10/290 (3.5%)	8/315 (2.8%)	1.21 (0.49-2.99)	0.67	0.65
SYNTAX score 23-32	7/310 (2.3%)	10/300 (3.8%)	0.61 (0.23-1.61)	0.32	
SYNTAX score 0-22	1/299 (0.3%)	6/275 (2.4%)	0.28 (0.02-1.20)	0.073	



C

Cause of deaths	CR	ICR	HR (95% CI)	*P*-value	Interaction *P*-value
Cardiac deaths					
PCI group	32/509 (6.7%)	46/388 (11.8%)	1.89 (1.20-2.98)	0.006	0.80
CABG group	23/551 (4.6%)	20/321 (6.6%)	1.51 (0.82-2.77)	0.18	
Sudden cardiac deaths					
PCI group	9/509 (1.9%)	15/388 (3.8%)	1.99 (0.86-4.60)	0.11	0.67
CABG group	7/551 (1.4%)	8/321 (2.5%)	1.94 (0.75-5.76)	0.21	
MI-related deaths					
PCI group	19/509 (4.1%)	17/388 (4.4%)	1.27 (0.66-2.44)	0.47	0.074
CABG group	2/551 (0.4%)	2/321 (0.7%)	1.66 (0.23-11.70)	0.61	
CHF/Other cardiac deaths					
PCI group	4/509 (0.8%)	14/388 (3.6%)	4.46 (1.47-13.56)	0.008	0.14
CABG group	14/551 (2.8%)	10/321 (3.3%)	1.31 (0.59-2.88)	0.51	

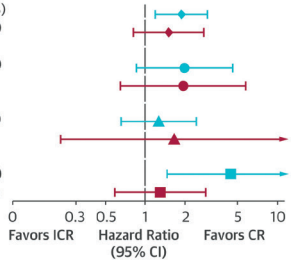


Figure 4. Hazard Ratios of CABG versus PCI Subgroup Analyses. (A) Cardiac cause of deaths within subgroups according to diabetes, left main (LM) or 3-vessel disease, and SYNTAX score. **(B)** Specific causes of cardiac deaths within subgroups according to diabetes, LM, or 3-vessel disease, and SYNTAX score. **(C)** Causes of deaths based on revascularization status (incomplete vs. complete) in PCI and CABG groups. CI, confidence interval; CR, complete revascularization; HR, hazard ratio; ICR, incomplete revascularization; other abbreviations as in Figures 1 and 2.

In multivariate analysis, PCI versus CABG treatment was not an independent predictor of all-cause death. Although, in the overall model, as well as in the separate PCI and CABG models, numerous baseline variables, such as older age and the presence of comorbidities, were independent predictors (Table 3). Moreover, procedural events such as incomplete revascularization, post-procedural prescription of medication as secondary prevention, and the occurrence of nonfatal adverse events were predictive of all-cause death. In separate models, results were largely similar, although incomplete revascularization, medically treated diabetes and left ventricular function were only predictors in the PCI model and not in the CABG model (Table 3). In contrast, renal failure and chronic obstructive pulmonary disease were only predictors in the CABG model.

Table2. Baseline Characteristics of the Patients in the SYNTAX Randomized Cohort Who Completed 5-Year Follow-Up.

	PCI (n = 871)		p Value	CABG (n = 805)		p Value
	Alive (n = 748)	Death (n = 123)		Alive (n = 708)	Death (n = 97)	
Demographics						
Male	581 (77.7)	82 (66.7)	0.008	563 (79.5)	81 (83.5)	0.36
Age, yrs	64.6 ± 9.6	69.7 ± 8.6	<0.0001	64.1 ± 9.5	70.6 ± 8.1	<0.0001
Medically treated diabetes	177 (23.7)	44 (35.8)	0.004	165 (23.3)	29 (29.9)	0.15
Any	112 (15.0)	24 (19.5)	0.20	96 (13.6)	16 (16.5)	0.43
Requiring insulin	65 (8.7)	20 (16.3)	0.009	69 (9.7)	13 (13.4)	0.26
Hypertension	540 (72.7)	98 (81.0)	0.054	534 (75.9)	80 (84.2)	0.07
Peripheral vascular disease	50 (6.7)	26 (21.1)	<0.0001	59 (8.3)	25 (25.8)	<0.0001
Unstable angina	206 (27.5)	46 (37.4)	0.025	194 (27.4)	26 (26.8)	0.90
Stabile angina	435 (58.2)	61 (49.6)	0.08	430 (60.7)	45 (46.4)	0.007
Creatinine >200 mmol/l	6 (0.8)	4 (3.3)	0.018	8 (1.1)	6 (6.2)	<0.0001
Pulmonary hypertension	7 (0.9)	1 (0.8)	0.90	6 (0.8)	3 (3.1)	0.049
Previous MI	217 (29.4)	54 (44.3)	0.001	227 (32.4)	36 (37.9)	0.28
Carotid artery disease	52 (7.0)	17 (13.8)	0.009	50 (7.1)	17 (17.5)	<0.0001
Chronic obstructive pulmonary disease	52 (7.0)	16 (13.0)	0.02	57 (8.1)	18 (18.6)	0.001
LVEF						
Moderate (30%–49%)	119 (16.3)	34 (28.3)	0.002	119 (17.0)	20 (20.6)	0.37
Poor (<30%)	5 (0.7)	7 (5.8)	<0.0001	12 (1.7)	5 (5.2)	0.028

Table 2. Continued.

Baseline anatomical and clinical scores						
SYNTAX score	27.9 ± 11.4	32.4 ± 11.3	<0.0001	29.0 ± 11.3	30.6 ± 12.3	0.19
Additive EuroScore	3.2 ± 2.3	5.3 ± 3.0	<0.0001	3.1 ± 2.3	4.9 ± 2.9	<0.0001
Total Parsonnet score	7.9 ± 6.6	12.3 ± 7.7	<0.0001	7.6 ± 6.3	13.1 ± 7.9	<0.0001
Left main disease	301 (40.2)	45 (36.6)	0.44	273 (38.6)	49 (50.5)	0.024
Procedural characteristics						
Bypass time (min)	—	—	—	84.8 ± 32.6	93.1 ± 48.1	0.046
No. of grafts	—	—	—	2.8 ± 0.7	2.6 ± 0.8	0.036
No. of distal anastomoses	—	—	—	3.2 ± 0.9	3.0 ± 1.0	0.026
No. of stents implanted	4.6 ± 2.3	5.0 ± 2.2	0.053	—	—	—
Staged procedure	97 (13.0)	27 (22.0)	0.008	—	—	—
Incomplete revascularization	317 (42.7)	71 (58.2)	0.001	260 (36.4)	38 (40.9)	0.40
Treatments at baseline						
ARB or ACE inhibitor	432 (57.8)	83 (67.5)	0.042	441 (62.3)	73 (75.3)	0.013
Beta-blocker	555 (74.2)	89 (72.4)	0.67	563 (79.5)	64 (66.0)	0.003
Amiodarone	8 (1.1)	4 (3.3)	0.054	5 (0.7)	1 (1.0)	0.73
Cardiac glycoside	5 (0.7)	3 (2.4)	0.056	4 (0.6)	3 (3.1)	0.012
Diuretics	163 (21.8)	46 (37.4)	<0.0001	149 (21.0)	31 (32.0)	0.016
Treatments at discharge						
Acetylsalicylic acid	641 (86.4)	56 (45.9)	<0.0001	593 (83.9)	32 (34.0)	<0.0001
Thienopyridine antiplatelet	238 (32.1)	34 (27.9)	0.35	94 (13.3)	2 (2.1)	0.002
ARB or ACE inhibitor	547 (73.1)	44 (35.8)	<0.0001	514 (72.6)	35 (36.1)	<0.0001
Beta-blocker	572 (76.4)	52 (42.6)	<0.0001	529 (74.9)	36 (37.1)	<0.0001
Amiodarone	13 (1.7)	7 (5.7)	0.006	15 (2.1)	4 (4.1)	0.22
Statin	631 (85.0)	51 (41.8)	<0.0001	610 (86.3)	28 (29.8)	<0.0001

Values are n (%) or mean ± SD.
ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; MI, myocardial infarction; other abbreviations as in Table 1.

Treatment with PCI versus CABG was an independent predictor of cardiac death (HR: 1.55; 95% CI: 1.0 to 2.33; p = 0.045) (Table 4). Furthermore, the independent predictors in the overall and PCI models for cardiac death were nearly identical as for all-cause death (Table 4). An additional predictor for cardiac events after PCI was the SYNTAX score. The CABG model included previous MI and bypass time as additional independent predictors, whereas other baseline characteristics no longer were predictors.

Nested registries. Baseline and procedural characteristics of patients alive at the end of follow-up and patients who died during follow-up are reported in the Supplemental Table 2. In the multivariate models that predicted all-cause and cardiac death, results were relatively similar to the randomized cohort, with a number of baseline, procedural, and post-procedural variables as independent predictors (Table 5). Of note, in the PCI registry, LM disease and the SYNTAX score were predictors.

Table 3. Independent Predictors of All-Cause Mortality in the SYNTAX Randomized Cohort.

	HR (95% CI)	p Value
SYNTAX randomized cohort		
Age (per 5-yr increase)	1.25 (1.15–1.36)	<0.0001
Medically treated diabetes	1.36 (1.01–1.84)	0.042
Peripheral vascular disease	2.04 (1.46–2.83)	<0.0001
LVEF poor (<30%)	4.47 (2.31–8.66)	<0.0001
Previous MI	1.31 (1.01–1.75)	0.044
Incomplete revascularization	1.37 (1.03–1.81)	0.029
Beta-blocker use at discharge	0.66 (0.47–0.93)	0.019
ARB or ACE inhibitor use at discharge	0.49 (0.35–0.69)	<0.0001
Acetylsalicylic acid use at discharge	0.47 (0.33–0.67)	<0.0001
Statin use at discharge	0.27 (0.19–0.39)	<0.0001
Nonfatal CVA during follow-up	2.07 (1.12–2.95)	0.032
Nonfatal MI during follow–up	3.86 (2.69–5.53)	<0.0001
PCI group		
Age (per 5-yr increase)	1.25 (1.11–1.40)	0.008
Medically treated diabetes	1.66 (1.09–2.53)	0.018
Peripheral vascular disease	2.77 (1.73–4.44)	<0.0001
LVEF poor (<30%)	2.26 (1.67–3.07)	<0.0001
LVEF moderate (30%–49%)	2.37 (1.54–3.63)	<0.0001
Incomplete revascularization	1.73 (1.17–2.58)	0.007
Beta-blocker use at discharge	0.59 (0.37–0.97)	0.036
ARB or ACE inhibitor use at discharge	0.43 (0.27–0.68)	<0.0001
Acetylsalicylic acid use at discharge	0.52 (0.32–0.85)	0.008
Statin use at discharge	0.43 (0.27–0.69)	0.001
Nonfatal MI during follow-up	5.49 (3.68–9.14)	<0.0001
CABG group		
Age (per 5-yr increase)	1.27 (1.09–1.48)	0.002
Peripheral vascular disease	2.01 (1.14–3.54)	0.016
Creatinine blood level >200 mmol/l	4.75 (1.38–16.41)	0.014
Chronic obstructive pulmonary disease	1.92 (1.05–3.48)	0.033
ARB or ACE inhibitor use at discharge	0.52 (0.28–0.94)	0.033
Acetylsalicylic acid use at discharge	0.39 (0.20–0.74)	0.004
Statin use at discharge	0.28 (0.20–0.43)	<0.0001
Nonfatal MI during follow-up	3.88 (1.60–9.39)	0.003

C-statistics for the models were: overall, 0.71 (95% CI: 0.68 to 0.75; p < 0.0001); PCI, 0.74 (95% CI: 0.69 to 0.79; p < 0.0001); CABG, 0.71 (95% CI: 0.65 to 0.76; p < 0.0001). Abbreviations as in Tables 1 to 3.

Table 4. Independent Predictors of Cardiac Mortality in the SYNTAX Randomized Cohort.

	HR (95% CI)	p Value
SYNTAX randomized cohort		
PCI treatment vs. CABG	1.55 (1.09–2.33)	0.045
Age (per 5-yr increase)	1.16 (1.04–1.31)	0.009
Peripheral vascular disease	2.55 (1.64–3.98)	<0.0001
LVEF poor (<30%)	5.08 (1.97–13.12)	0.001
LVEF moderate (30%–49%)	1.76 (1.15–2.69)	0.009
Previous MI	1.69 (1.14–2.50)	0.010
Incomplete revascularization	1.67 (1.13–2.45)	0.010
ARB or ACE inhibitor use at discharge	0.58 (0.37–0.92)	0.020
Acetylsalicylic acid use at discharge	0.54 (0.34–0.86)	0.010
Statins use at discharge	0.25 (0.16–0.41)	<0.0001
Nonfatal MI during follow-up	6.16 (3.98–9.53)	<0.0001
PCI group		
Peripheral vascular disease	2.79 (1.54–5.71)	0.001
LVEF poor (<30%)	1.83 (1.26–3.15)	0.006
LVEF moderate (30%–49%)	3.06 (1.84–5.57)	<0.0001
SYNTAX score	1.03 (1.01–1.05)	0.016
Incomplete revascularization	1.83 (1.15–3.24)	0.011
ARB or ACE inhibitor use at discharge	0.48 (0.27–0.81)	0.007
Acetylsalicylic acid use at discharge	0.46 (0.26–0.88)	0.018
Statins use at discharge	0.39 (0.21–0.58)	<0.0001
Nonfatal MI during follow-up	6.79 (4.24–10.72)	<0.0001
CABG group		
Peripheral vascular disease	4.10 (1.88–8.97)	<0.0001
Creatinine blood level >200 mmol/l	5.65 (1.19–26.81)	0.029
Prior MI	2.35 (1.14–4.81)	0.020
Bypass time (min)	1.01 (1.00–1.02)	0.009
Acetylsalicylic acid use at discharge	0.37 (0.16–0.83)	0.016
Statins use at discharge	0.29 (0.18–0.44)	<0.0001
Nonfatal MI during follow-up	7.25 (2.39–22.02)	<0.0001

C-statistics for the models were: overall, 0.72 (95% CI: 0.67 to 0.77; $p < 0.0001$); PCI, 0.70 (95% CI: 0.64 to 0.76; $p < 0.0001$); CABG, 0.75 (95% CI: 0.66 to 0.83; $p < 0.0001$).
Abbreviations as in Tables 1 to 3.

Table 5. Independent Predictors of All-Cause and Cardiac Mortality in the SYNTAX Nested Registries.

	HR (95% CI)	p Value
PCI registry		
All-cause mortality		
Age (per 5-yr increase)	1.44 (1.23–1.68)	<0.0001
Chronic obstructive pulmonary disease	1.90 (1.01–3.59)	0.047
LVEF poor (<30%)	3.19 (1.33–7.65)	0.009
Left main disease	2.29 (1.25–4.19)	0.007
Previous MI	1.88 (1.04–3.41)	0.037
Beta-blocker use at discharge	0.52 (0.28–0.96)	0.038
Nonfatal MI during follow-up	2.50 (1.07–5.83)	0.033
Cardiac mortality		
Age (per 5-yr increase)	1.53 (1.11–2.09)	0.008
Medically treated diabetes	5.56 (1.40–22.03)	0.015
Creatinine blood level >200 mmol/l	12.18 (1.51–80.44)	0.019
Left main disease	5.66 (1.52–21.10)	0.010
Previous MI	6.65 (1.91–23.15)	0.003
SYNTAX score	1.09 (1.04–1.14)	<0.0001
CABG registry		
All-cause mortality		
Age (per 5-yr increase)	1.21 (1.04–1.41)	0.015
Medically treated diabetes	2.22 (1.34–3.70)	0.002
Chronic obstructive pulmonary disease	3.32 (1.79–6.17)	<0.0001
LVEF moderate (30%–49%)	2.24 (1.33–3.78)	0.002
Procedure time (min)	1.01 (1.00–1.02)	<0.0001
Acetylsalicylic acid use at discharge	0.41 (0.22–0.76)	0.004
Nonfatal MI during follow-up	2.54 (1.08–5.96)	0.033
Cardiac mortality		
LVEF moderate (30%–49%)	4.05 (1.66–9.87)	0.002
Acetylsalicylic acid use at discharge	0.30 (0.18–0.80)	0.009
Nonfatal MI during follow-up	5.29 (1.52–18.41)	0.016

Abbreviations as in Tables 1 to 3.

DISCUSSION

The present study provides crucial perspectives on causes of death within the SYNTAX trial at 5-year follow-up (Central Illustration). Our findings indicate that treatment with CABG significantly reduces cardiac death compared with PCI, which was due exclusively to a lower incidence of MI-related death. Particularly in patient groups with 3VD and/or a SYNTAX score >=33, cardiac

death was significantly higher after PCI than CABG. Numerous patient baseline characteristics were independent predictors of death, although procedural characteristics (e.g., incomplete revascularization), the use of specific medications, and events during follow-up (e.g., nonfatal MI) also contributed in predicting all-cause and cardiac death.

Similarly to previous randomized trials that compared CABG with PCI using bare-metal stents, long-term rates of all-cause mortality were comparable between CABG and PCI (15,16). Despite the inclusion of patients with more complex disease, such as LM and 3VD, rates of all-cause death in the SYNTAX trial were comparable to that of previous trials. For the patients treated with CABG, this might be the result of more refined operative techniques and conduit choices, among others. For patients who underwent PCI, factors that might have contributed to lowering adverse events during follow-up were the first-time implantation of DES and the increased use of dual antiplatelet therapy. In a recent report on trends in long-term, cause-specific death after PCI, Spoon et al. (17) found that rates of deaths were similar from 1991 to 2012, whereas in more recent procedures, deaths occurred less often from cardiac causes.

Unfortunately, many previous analyses from randomized trials were limited by few specifics on the causes of cardiac deaths. Anecdotal evidence suggested that the advantage of CABG over medical therapy was particularly driven by reduced rates of sudden cardiac death (5,6,18). A recent analysis of deaths that occurred in the STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that CABG further reduced rates of fatal MI (18). Comparative analyses regarding causes of death between CABG and PCI are restricted to a single observational study of approximately 10,000 patients with 140 sudden cardiac deaths, in which there was no difference in the rate of sudden cardiac death after CABG versus PCI (19).

In the present analysis, there was a significant difference in rates of cardiac death between CABG and PCI. Rates of sudden cardiac death were comparable, but MI-related deaths were significantly lower after CABG. The majority of deaths among patients who underwent PCI were related to MI, which accounted for nearly 50% of the total cardiac deaths. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, the reduction in the composite of death, stroke, and MI with CABG versus medical therapy was driven largely by a reduction in MI, whereas the PCI versus medical therapy analysis showed similar rates of MI among the 2 groups (20). These findings emphasize the importance of MI reduction after PCI. Overall, use of the newer-generation DES (21) and default use of fractional

flow reserve (22) are considered to reduce the rate of MI and death by reducing events of stent thrombosis and restenosis in more contemporary trials. The impact of prolonged use and the exact duration of dual antiplatelet therapy on ischemic events remain topics of debate (23,24). Nevertheless, de novo lesions in patients who previously underwent PCI can progress to cause MI and subsequently death, whereas after CABG, the significance of such lesions with an existing patent bypass graft is limited. Even with the use of second-generation DES, the rate of spontaneous MI continues to be higher after PCI than CABG (25). Moreover, the lower rates of MI-related deaths with CABG might result from more complete revascularization and subsequently lower areas of ischemic myocardium (6,26). These concepts were validated in several studies that demonstrated that CABG had more durable protection against MI in patients with extensive CAD (16,27,28).

Because incomplete revascularization with PCI occurs more often in patients with highly complex lesions, and specifically chronic total occlusions (26,29), the present results emphasize these differences between CABG and PCI in the cardiac death subgroup analyses according to SYNTAX score tertiles. In the highest SYNTAX score tertiles, patients who underwent PCI had a higher risk of MI-related death and sudden cardiac deaths. Patients with complex disease undergoing PCI have a continued higher risk of stent thrombosis, which is related to cardiac death (30). In patients with complex disease and incomplete revascularization, lesions without revascularization have a considerable risk of progressing to acute events, a similar finding as in an analysis of the BARI trial that showed that revascularization versus no revascularization reduced the rate of sudden cardiac death (6). Moreover, progression of disease in patients with complex disease and higher SYNTAX scores may be enhanced because of a higher risk profile (e.g., diabetes, hypertension, and so on) that furthermore increases the risk of adverse events (31). These considerations contributed to the selection of less complex LM disease in the EXCEL (Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) randomized comparison between CABG and LM stenting with current generation DES.

In subgroups according to diabetes, the difference between PCI and CABG in cardiac death was greater in diabetic patients than in nondiabetic patients, whereas the difference in all-cause death was not significant in diabetic patients (32). This is notable in the BARI publication (33), but not in the results of the recent FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, which results were in favor of CABG in terms of all-cause death and comparable outcomes in

cardiovascular death (34). This may reflect the relatively low number of events of cardiac or cardiovascular death and the play of chance that may play a role. In other subgroup analyses, the significant increases in cardiac deaths that were observed after PCI in patients with 3VD strengthens the finding that these patients particularly benefited from CABG (35). Conversely, consistent with other studies of patients with LM diseases, cardiac death was not different between PCI and CABG (25,36), justifying the hypothesis on which the current EXCEL trial is based (NCT01205776).

Multivariate models identified several distinct variables associated with long-term all-cause and cardiac death that may aid decisions regarding revascularization strategies. In comparison with previously published studies that identified predictors of long-term mortality (33,37,38), our results add significantly to the current body of evidence. Longterm analyses of all-cause mortality may lose accuracy in determining the relevance of myocardial revascularization to the occurrence of death, whereas analysis of cardiac death as adjudicated by a CEC may provide a more clear distinction between death as a result of comorbidities or as the consequence of CAD. Furthermore, the majority of models to predict death included only preoperative values. The present analyses also emphasized the importance of nonfatal adverse events (stroke and MI) as predictors of future fatal events. We identified that a nonfatal stroke was a significant predictor of death, which corresponds with the association between stroke and subsequent increased risk not only of repeated stroke, but also of the combined risk of stroke and MI (39). In addition, a nonfatal MI was associated with an increased risk of all-cause and cardiac mortality. This might be the result of progressive heart failure because our findings also showed that patients with a moderate or poor left ventricular ejection fraction and a history of MI are at an increased risk of MI-related death. Therefore, prevention of MI after treatment with PCI, but also after CABG, is of critical importance for survival. As shown in our multivariate analyses, as well as in several other studies, the importance of secondary prevention medication is essential in this regard. Iqbal et al. (40) recently showed that the impact of secondary prevention medication was even larger than the impact of performing PCI or CABG in patients with complex CAD. Guideline-directed medical therapy should be a principal strategy for all patients with CAD, as also recently shown in an analysis of BARI 2D data (41). This information on predictors may be particularly useful for the Heart Team currently when both PCI and CABG are excellent treatment options; the Heart Team should not only determine the most optimal revascularization strategy, but which strategy might also be useful when integrated into the postprocedural phase (7).

STUDY LIMITATIONS. The present study represents a post-hoc analysis; therefore, the results should be regarded as exploratory and hypothesis-generating. Moreover, a great number of subgroup analyses have been reported, so results should be interpreted with caution because some differences may be the results of chance (42). Although the SYNTAX trial was an all-comers randomized trial, inclusion of patients in a randomized trial is limited to specific inclusion and exclusion criteria; therefore, the external validity, which reflects actual patients in the real-world, may be suboptimal.

Despite the primarily used SYNTAX trial classifications, the determination of cause-specific death could not always be established. This is particularly relevant to the subcategories of cardiac death in which absolute precision may not always be possible. However, bias was limited by event adjudication by a blinded committee of physician experts using previous standardized definitions.

Autopsy was performed in a low number of cases (n = 38, 10.7%); therefore, the rate of death related to MI could be underestimated, considering that MI might be involved in the process of heart failure and cardiac rupture, as well as sudden cardiac death.

We did not have information on post-procedural occurrence of additional co-morbidities, which could affect the established groups of predictors.

Although medication use was recorded throughout different time points during follow-up, there were no data on compliance rates or on reasons for discontinuation of medication. Moreover, at later follow-up with longer periods between collection of medication data (e.g., 2 years), we were unable to determine the exact date of medication discontinuation. Therefore, we could not assess the impact of medication use during follow-up on death rates.

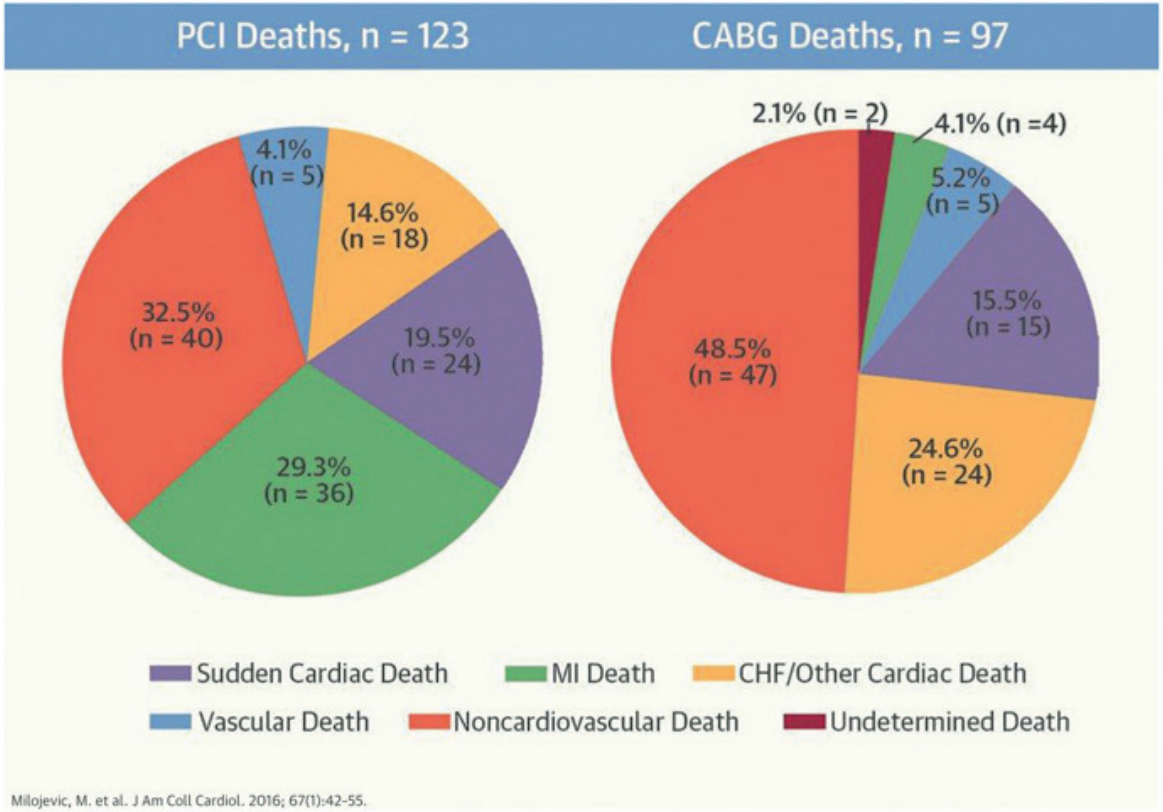
CONCLUSIONS

For patients with complex CAD, CABG compared with PCI did not reduce all-cause death, but was shown to be associated with a significantly reduced rate of cardiac death that was driven primarily by a reduction of death as a consequence of MI. This reduction was greatest in patients with diabetes, 3VD, or a SYNTAX score >=33. Although PCI is becoming a more acceptable revascularization strategy for patients with LM or 3VD, treatments following PCI should target reducing post-revascularization spontaneous MI, because this remains the leading cause of death after PCI.

CLINICAL PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with complex coronary disease, CABG was associated with a lower rate of cardiac death after 5 years than PCI, and patients who underwent PCI with first-generation DES were at higher risk of fatal MI than those managed with CABG.

TRANSLATIONAL OUTLOOK: Additional randomized studies in patients undergoing PCI with newer generation DES should examine predictors of MI-related death.



CENTRAL ILLUSTRATION. Causes of Deaths in the SYNTAX Randomized Cohort: PCI and CABG Comparison. After percutaneous coronary intervention (PCI), the leading cause of cardiovascular death was myocardial infarction (MI)-related death. After coronary artery bypass grafting (CABG), the leading cause of cardiovascular death was congestive heart failure (CHF), arrhythmia, or other causes (e.g., arrhythmia and all other cardiac deaths).

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SUPPLEMENTAL MATERIAL

Baseline variables included in univariate analyses to predict death.

In the overall model including both PCI and CABG patients, the following variables were added: male gender, age per 5 years, medically treated diabetes, hypertension, hyperlipidemia, peripheral vascular disease, unstable angina, history of stroke or transient ischemic attack, creatinine blood level >200 micromol/L, prior myocardial infarction, carotid artery disease, chronic obstructive pulmonary disease, poor left ventricular ejection fraction <30%, moderate left ventricular ejection fraction 30-49%, left main coronary disease, non-fatal stroke during follow-up, non-fatal myocardial infarction during follow-up, incomplete revascularization, beta-blocker at discharge, angiotensin converting enzyme or angiotensin renin blocker inhibitor medication at discharge, calcium channel blockers at discharge, acetylsalicylic acid at discharge, thienopyridine at discharge, diuretics medication at discharge, statins at discharge, and PCI versus CABG treatment.

Additional variables added in the separate PCI model: SYNTAX score, number of stents implanted, total stent length implanted and staged procedure. The variable 'PCI versus CABG treatment' was deleted in this model.

Additional variables added in the separate CABG model: SYNTAX score, procedure time, bypass time, number of grafts and number of distal anastomoses. The variable 'PCI versus CABG treatment' was deleted in this model.

Supplemental Table 1. Baseline characteristics of the patients in the SYNTAX Randomized Cohort who completed 5-year follow-up.

	PCI (n=871)			CABG (n=805)		
Baseline characteristics	**Alive (n=748)**	**Death (n=123)**	**P Value**	**Alive (n=708)**	**Death (n=97)**	**P Value**
Demographics						
Male	581 (77.7)	82 (66.7)	0.008	563 (79.5)	81 (83.5)	0.36
Age	64.6 ± 9.6	69.7 ± 8.6	<0.0001	64.1 ± 9.5	70.6 ± 8.1	<0.0001
BMI (kg/m2)	28.2 ± 4.7	27.9 ± 5.3	0.50	27.9 ± 4.5	27.5 ±4.4	0.39
Waist diameter, cm	85.0 ± 27.3	84.6 ± 26.8	0.88	85.4 ± 27.4	87.4 ± 25.8	0.54
Medical treated diabetes	177 (23.7)	44 (35.8)	0.004	165 (23.3)	29 (29.9)	0.15
Any	112 (15.0)	24 (19.5)	0.20	96 (13.6)	16 (16.5)	0.43
Requiring insulin	65 (8.7)	20 (16.3)	0.009	69 (9.7)	13 (13.4)	0.26
Hypertension	540 (72.7)	98 (81.0)	0.054	534 (75.9)	80 (84.2)	0.07
Hyperlipidemia	590 (79.5)	89 (73.0)	0.10	554 (79.0)	69 (71.9)	0.11
Peripheral vascular disease	50 (6.7)	26 (21.1)	<0.0001	59 (8.3)	25 (25.8)	<0.0001
Current smoker	130 (17.4)	25 (20.3)	0.43	151 (21.4)	19 (20.0)	0.75
Unstable angina	206 (27.5)	46 (37.4)	0.025	194 (27.4)	26 (26.8)	0.90
Stabile angina	435 (58.2)	61 (49.6)	0.08	430 (60.7)	45 (46.4)	0.007
History of stroke or TIA	51 (6.8)	11 (8.9)	0.40	61 (8.7)	13 (13.5)	0.12
Creatinine > 200 micromol/L	6 (0.8)	4 (3.3)	0.018	8 (1.1)	6 (6.2)	<0.0001
Pulmonary hypertension	7 (0.9)	1 (0.8)	0.90	6 (0.8)	3 (3.1)	0.049
Prior MI	217 (29.4)	54 (44.3)	0.001	227 (32.4)	36 (37.9)	0.28
Carotid artery disease	52 (7.0)	17 (13.8)	0.009	50 (7.1)	17 (17.5)	<0.0001
Chronic obstructive pulmonary disease	52 (7.0)	16 (13.0)	0.02	57 (8.1)	18 (18.6)	0.001
LVEF						
Moderate (30%-49%)	119 (16.3)	34 (28.3)	0.002	119 (17.0)	20 (20.6)	0.37
Poor (<30%)	5 (0.7)	7 (5.8)	<0.0001	12 (1.7)	5 (5.2)	0.028
Baseline anatomical and clinical scores						
SYNTAX Score	27.9 ± 11.4	32.4 ± 11.3	<0.0001	29.0 ± 11.3	30.6 ± 12.3	0.19
Additive EuroScore	3.2 ± 2.3	5.3 ± 3.0	<0.0001	3.1 ± 2.3	4.9 ± 2.9	<0.0001
Logistic EuroScore	3.3 ± 4.2	6.3 ± 5.6	<0.0001	3.3 ± 3.3	7.2 ± 8.1	<0.0001
Total Parsonnet score	7.9 ± 6.6	12.3 ± 7.7	<0.0001	7.6 ± 6.3	13.1 ± 7.9	<0.0001
Left Main Coronary disease	301 (40.2)	45 (36.6)	0.44	273 (38.6)	49 (50.5)	0.024
Left arterial dominance	134 (17.9)	24 (19.5)	0.67	107 (15.1)	20 (20.6)	0.16
Procedural characteristics						
Emergency treatment	9 (1.2)	1 (0.8)	0.71	6 (0.8)	2 (2.1)	0.26
Procedure time (min)	-	-	-	206.1 ± 59.1	220.9 ± 82.6	0.095

Bypass time (min)	-	-	-	84.8 ± 32.6	93.1 ± 48.1	0.046
Cross clamp time (min)	-	-	-	55.8 ± 37.3	52.8 ± 22.3	0.50
Off-pump surgery	-	-	-	99 (13.9)	11 (1.8)	0.59
Complete arterial	-	-	-	143 (20.0)	14 (15.1)	0.25
Bilateral internal mammary artery use	-	-	-	200 (28.3)	20 (21.7)	0.19
Number of grafts	-	-	-	2.8 ± 0.7	2.6 ± 0.8	0.036
Arterial grafts	-	-	-	1.4 ± 0.7	1.3 ± 0.5	0.17
Venous grafts	-	-	-	1.4 ± 0.9	1.3 ± 0.9	0.76
Number of distal anastomoses	-	-	-	3.2 ± 0.9	3.0 ± 1.0	0.026
Number of stents implanted	4.6 ± 2.3	5.0 ± 2.2	0.053	-	-	-
Total stent length implanted (mm)	85.1 ± 48.3	91.8 ± 46.4	0.15	-	-	-
Long stenting (>100mm)	244 (32.7)	57 (39.2)	0.16	-	-	-
Total overlapping stents	0.6 ± 0.6	0.7 ± 0.7	0.29	-	-	-
Staged procedure	97 (13.0)	27 (22.0)	0.008	-	-	-
Incomplete revascularization	317 (42.7)	71 (58.2)	0.001	260 (36.4)	38 (40.9)	0.40
Treatments at baseline						
Acetylsalicylic acid	653 (87.3)	105 (85.4)	0.55	571 (80.6)	75 (77.3)	0.44
Thienopyridine antiplatelet	451 (60.3)	82 (66.7)	0.18	185 (26.1)	22 (22.7)	0.47
Antiplatelet-other	33 (4.4)	9 (7.3)	0.16	44 (6.2)	5 (5.2)	0.68
Coumadin derivative	13 (1.7)	3 (2.4)	0.59	15 (2.1)	5 (5.2)	0.07
ARB or ACE inhibitor	432 (57.8)	83 (67.5)	0.042	441 (62.3)	73 (75.3)	0.013
β-Blocker	555 (74.2)	89 (72.4)	0.67	563 (79.5)	64 (66.0)	0.003
Calcium channel blockers	203 (27.1)	35 (28.5)	0.76	177 (25.0)	26 (26.8)	0.70
Nitrates	269 (36.0)	46 (37.4)	0.76	288 (40.7)	40 (41.2)	0.92
Amiodarone	8 (1.1)	4 (3.3)	0.054	5 (0.7)	1 (1.0)	0.73
Statin	563 (75.3)	85 (69.1)	0.15	545 (77.0)	69 (71.7)	0.20
Cardiac glycoside	5 (0.7)	3 (2.4)	0.056	4 (0.6)	3 (3.1)	0.012
Diuretics	163 (21.8)	46 (37.4)	<0.0001	149 (21.0)	31 (32.0)	0.016
H2-receptors blockers	78 (10.4)	9 (7.3)	0.29	67 (9.5)	11 (11.3)	0.56
Treatments at discharge						
Acetylsalicylic acid	641 (86.4)	56 (45.9)	<0.0001	593 (83.9)	32 (34.0)	<0.0001
Thienopyridine antiplatelet	238 (32.1)	34 (27.9)	0.35	94 (13.3)	2 (2.1)	0.002
Antiplatelet-other	33 (4.4)	2 (1.6)	0.16	23 (3.3)	2 (2.1)	0.52
Coumadin derivative	41 (5.5)	3 (2.5)	0.17	39 (5.5)	4 (4.1)	0.57
ARB or ACE inhibitor	547 (73.1)	44 (35.8)	<0.0001	514 (72.6)	35 (36.1)	<0.0001
β-Blocker	572 (76.4)	52 (42.6)	<0.0001	529 (74.9)	36 (37.1)	<0.0001
Calcium channel blockers	188 (25.1)	24 (19.7)	0.19	168 (23.8)	17 (17.5)	0.17
Nitrates	112 (15.0)	17 (13.9)	0.76	66 (9.3)	8 (8.2)	0.72

Amiodarone	13 (1.7)	7 (5.7)	0.006	15 (2.1)	4 (4.1)	0.22
Statin	631 (85.0)	51 (41.8)	<0.0001	610 (86.3)	28 (29.8)	<0.0001
Cardiac glycoside	12 (1.6)	4 (3.3)	0.20	9 (1.3)	2 (2.1)	0.53
Diuretics	197 (26.3)	25 (20.5)	0.17	210 (29.7)	22 (22.7)	0.15
H2-receptors blockers	90 (12.0)	11 (9.0)	0.33	77 (10.9)	8 (8.2)	0.42

Values are shown as mean ± SD or n (%). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; BMI, body mass index; MI, myocardial infarction; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; TIA, transient ischemic attack.

Supplemental Table 2. Baseline characteristics of the patients enrolled in the SYNTAX Registries Cohort who completed 5-year follow-up.

	PCI (n=184)			CABG (n=607)		
Baseline characteristics	**Alive (n=127)**	**Death (n=57)**	**P Value**	**Alive (n=528)**	**Death (n=79)**	**P Value**
Demographics						
Male	94 (70.7)	40 (70.2)	0.94	454 (80.4)	66 (83.5)	0.50
Age	69.0 ± 10.6	76.3 ± 8.4	<0.0001	65.2 ± 9.3	69.2 ± 9.1	<0.0001
BMI (kg/m2)	27.8 ± 5.3	28.2 ± 5.9	0.70	28.1 ± 4.6	27.4 ± 4.5	0.21
Waist diameter, cm	88.2 ± 24.3	82.1 ± 34.5	0.24	81.2 ± 30.1	80.0 ± 28.3	0.77
Medical treated diabetes	43 (32.3)	25 (43.9)	0.13	155 (27.4)	36 (45.6)	0.001
Any	25 (18.8)	14 (24.6)	0.37	108 (19.1)	22 (27.8)	0.070
Requiring insulin	18 (13.5)	11 (19.3)	0.11	47 (8.3)	14 (17.7)	0.008
Hypertension	105 (79.5)	38 (66.7)	0.058	402 (72.3)	63 (81.8)	0.076
Hyperlipidemia	95 (72.0)	32 (56.1)	0.033	427 (77.5)	53 (68.8)	0.093
Peripheral vascular disease	19 (14.3)	12 (21.1)	0.25	69 (12.2)	20 (25.3)	0.002
Current smoker	18 (13.6)	3 (5.6)	0.11	126 (22.4)	14 (18.2)	0.40
Unstable angina	45 (33.3)	27 (47.4)	0.066	124 (21.9)	15 (19.0)	0.55
Stabile angina	65 (48.9)	24 (42.1)	0.39	355 (62.8)	50 (63.3)	0.94
History of stroke or TIA	15 (11.3)	12 (21.1)	0.077	52 (9.3)	9 (11.4)	0.54
Creatinine > 200 micromol/L	7 (5.3)	4 (7.0)	0.63	10 (1.8)	3 (3.8)	0.23
Pulmonary hypertension	2 (1.5)	3 (5.3)	0.14	4 (0.7)	3 (3.8)	0.013
Prior MI	50 (38.2)	25 (45.5)	0.35	182 (33.1)	29 (36.7)	0.52
Carotid artery disease	13 (9.8)	7 (12.3)	0.61	64 (11.3)	15 (19.0)	0.042
COPD	18 (13.5)	19 (33.3)	0.002	37 (6.5)	14 (17.7)	0.001
LVEF						
Moderate (30%-49%)	34 (26.6)	13 (23.6)	0.68	121 (22.2)	29 (36.7)	0.005
Poor (<30%)	5 (3.9)	6 (10.9)	0.068	20 (3.7)	7 (8.9)	0.034
Baseline anatomical and clinical scores						
SYNTAX Score	26.1 ± 11.2	31.3 ± 15.2	0.025	34.6 ± 13.4	37.3 ± 13.4	0,09
Additive EuroScore	5.1 ± 3.0	7.6 ± 3.4	<0.0001	3.6 ± 2.6	4.8 ± 2.6	<0.0001
Left Main Coronary disease	47 (35.3)	32 (56.1)	0.008	270 (47.8)	36 (45.6)	0.71
Left arterial dominance	24 (18.0)	12 (21.1)	0.63	79 (14.0)	9 (11.4)	0.53
Procedural characteristics						
Emergency treatment	4 (3.0)	4 (7.0)	0.29	14 (2.5)	2 (2.5)	0.98
Procedure time (min)	-	-	-	213.1 ± 58.2	224.7 ± 88.0	0.26
Bypass time (min)	-	-	-	92.9 ± 32.7	99.6 ± 48.9	0.28
Cross clamp time (min)	-	-	-	59.3 ± 25.2	61.2 ± 38.8	0.71

Off-pump surgery	-	-	-	106 (18.8)	14 (17.7)	0.82
Complete arterial	-	-	-	63 (11.2)	9 (11.4)	0.95
Bilateral IMA use	-	-	-	96 (17.1)	8 (10.3)	0.12
Number of grafts	-	-	-	2.9 ± 0.8	2.7 ± 0.8	0.20
Arterial grafts	-	-	-	1.3 ± 0.7	1.2 ± 0.6	0.098
Venous grafts	-	-	-	1.7 ± 1.0	1.6 ± 1.1	0.55
Number of distal anastomoses	-	-	-	3.5 ± 0.9	3.5 ± 1.0	0.74
Number of stents implanted	3.2 ± 1.9	3.0 ± 1.6	0.26	-	-	-
Total stent length (mm)	61.3 ± 45.1	52.3 ± 30.1	0.059	-	-	-
Long stenting (>100mm)	19 (14.4)	4 (7.1)	0.16	-	-	-
Total overlapping stents	0.4 ± 0.6	0.4 ± 0.5	0.75	-	-	-
Staged procedure	18 (13.3)	7 (12.3)	0.84	-	-	-
Incomplete revascularization	84 (63.2)	41 (71.9)	0.24	133 (23.5)	30 (38.0)	0.006
Treatments at baseline						
Acetylsalicylic acid	107 (80.5)	52 (91.1)	0.065	423 (74.9)	58 (73.4)	0.78
Thienopyridine antiplatelet	98 (73.7)	40 (70.2)	0.62	94 (16.6)	10 (12.7)	0.37
Antiplatelet-other	13 (9.8)	5 (8.8)	0.83	48 (8.5)	8 (10.1)	0.63
Coumadin derivative	7 (5.3)	2 (3.5)	0.60	20 (3.5)	5 (6.3)	0.23
ARB or ACE inhibitor	78 (58.6)	32 (56.1)	0.75	313 (55.4)	55 (69.6)	0.017
β-Blocker	95 (71.4)	33 (57.9)	0.068	441 (78.1)	57 (72.2)	0.24
Calcium channel blockers	37 (27.8)	21 (36.8)	0.22	153 (27.1)	26 (32.9)	0.28
Nitrates	51 (38.3)	32 (56.1)	0.023	244 (43.2)	39 (49.4)	0.30
Amiodarone	0	3 (5.3)	0.008	13 (2.3)	3 (3.8)	0.42
Statin	86 (64.7)	36 (63.2)	0.84	398 (70.4)	53 (67.1)	0.54
Cardiac glycoside	5 (3.8)	2 (3.5)	0.93	4 (0.7)	2 (2.5)	0.11
Diuretics	47 (35.3)	28 (49.1)	0.075	128 (22.7)	34 (43.0)	<0.0001
H2-receptors blockers	6 (4.5)	3 (5.3)	0.82	50 (8.8)	7 (8.9)	0.99
Treatments at discharge						
Acetylsalicylic acid	125 (92.6)	53 (93.0)	0.92	506 (89.6)	63 (79.7)	0.011
Thienopyridine antiplatelet	124 (91.9)	54 (94.7)	0.48	98 (17.3)	11 (13.9)	0.45
Antiplatelet-other	8 (5.9)	5 (8.8)	0.47	35 (6.2)	4 (5.1)	0.69
Coumadin derivative	4 (3.0)	3 (5.3)	0.44	50 (8.8)	12 (15.2)	0.074
ARB or ACE inhibitor	86 (63.7)	37 (64.9)	0.87	286 (50.6)	35 (44.3)	0.29
β-Blocker	101 (74.8)	34 (59.6)	0.036	455 (80.5)	56 (70.9)	0.047
Calcium channel blockers	35 (25.9)	17 (29.8)	0.58	127 (22.5)	14 (17.7)	0.34
Nitrates	38 (28.1)	22 (38.6)	0.15	84 (14.9)	16 (20.3)	0.22
Amiodarone	1 (0.7)	4 (7.0)	0.013	70 (12.4)	9 (11.4)	0.80
Statin	99 (73.3)	39 (68.4)	0.49	388 (68.7)	52 (65.8)	0.61

Cardiac glycoside	2 (1.5)	2 (3.5)	0.37	7 (1.2)	2 (2.5)	0.36
Diuretics	43 (31.9)	26 (45.6)	0.069	227 (40.2)	41 (51.9)	0.048
H2-receptors blockers	11 (8.1)	6 (10.5)	0.60	112 (19.8)	16 (20.3)	0.93

Values are shown as mean ± SD or n (%). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; BMI, body mass index; MI, myocardial infarction; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; TIA, transient ischemic attack; IMA, internal mammary artery; COPD, chronic obstructive pulmonary disease.

Chapter 8

Stroke Rates Following Surgical Versus Percutaneous Coronary Revascularization

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ABSTRACT

BACKGROUND: Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are used for coronary revascularization in patients with multivessel and left main coronary artery disease. Stroke is among the most feared complications of revascularization. Due to its infrequency, studies with large numbers of patients are required to detect differences in stroke rates between CABG and PCI.

OBJECTIVES: This study sought to compare rates of stroke after CABG and PCI and the impact of procedural stroke on long-term mortality.

METHODS: We performed a collaborative individual patient-data pooled analysis of 11 randomized clinical trials comparing CABG with PCI using stents; ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease) (n = 450), ARTS (Arterial Revascularization Therapy Study) (n = 1,205), MASS II (Medicine, Angioplasty, or Surgery Study) (n = 408), SoS (Stent or Surgery) trial (n = 988), SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (n = 1,800), PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (n = 600), FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial (n = 1,900), VA CARDS (Coronary Artery Revascularization in Diabetes) (n = 198), BEST (Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) (n = 880), NOBLE (Percutaneous Coronary Angioplasty Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis) trial (n = 1,184), and EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (n = 1,905). The 30-day and 5-year stroke rates were compared between CABG and PCI using a random effects Cox proportional hazards model, stratified by trial. The impact of stroke on 5-year mortality was explored.

RESULTS: The analysis included 11,518 patients randomly assigned to PCI (n = 5,753) or CABG (n = 5,765) with a mean follow-up of 3.8 ± 1.4 years during which a total of 293 strokes occurred. At 30 days, the rate of stroke was 0.4% after PCI and 1.1% after CABG (hazard ratio (HR): 0.33; 95% confidence interval (CI): 0.20 to 0.53; $p < 0.001$). At 5-year follow-up, stroke remained significantly lower after PCI than after CABG (2.6% vs. 3.2%; HR: 0.77; 95% CI: 0.61 to 0.97;

p = 0.027). Rates of stroke between 31 days and 5 years were comparable: 2.2% after PCI versus 2.1% after CABG (HR: 1.05; 95% CI: 0.80 to 1.38; p = 0.72). No significant interactions between treatment and baseline clinical or angiographic variables for the 5-year rate of stroke were present, except for diabetic patients (PCI: 2.6% vs. CABG: 4.9%) and nondiabetic patients (PCI: 2.6% vs. CABG: 2.4%) (p for interaction = 0.004). Patients who experienced a stroke within 30 days of the procedure had significantly higher 5-year mortality versus those without a stroke, both after PCI (45.7% vs. 11.1%, p < 0.001) and CABG (41.5% vs. 8.9%, p < 0.001).

CONCLUSIONS: This individual patient-data pooled analysis demonstrates that 5-year stroke rates are significantly lower after PCI compared with CABG, driven by a reduced risk of stroke in the 30-day post-procedural period but a similar risk of stroke between 31 days and 5 years. The greater risk of stroke after CABG compared with PCI was confined to patients with multivessel disease and diabetes. Five-year mortality was markedly higher for patients experiencing a stroke within 30 days after revascularization.

INTRODUCTION

Numerous randomized clinical trials have compared coronary artery bypass grafting (CABG) and percutaneous coronary inter-vention (PCI) for treating coronary artery disease; first in the era of balloon angioplasty, subsequently with the use of bare-metal stents (BMS) (1,2), and most recently with use of drug-eluting stents (DES) (3). With improving technology and techniques of PCI, trials have increasingly focused on more complex patients with multivessel disease (MVD), left main (LM) disease, and diabetes.

Several studies have suggested that CABG versus PCI is associated with a significant increase of procedural stroke (1), a devastating outcome with substantial mortality, morbidity, and reduced quality of life. To date, there is a lack of conclusive evidence on the exact incidence and consequences of stroke following either CABG or PCI because individual randomized trials lacked sufficient power to detect small but meaningful differences between CABG and PCI (4). In a recent collaborative analysis of 11 randomized trials of patients with multivessel or LM coronary artery disease who were randomly assigned to CABG or PCI, we found significant differences in 5-year all-cause mortality in favor of CABG over PCI in patients with MVD and diabetes, whereas no differences were seen among patients with MVD without diabetes and in those with LM disease (5). Beyond mortality, it is important to consider endpoints that significantly impact quality of life, including stroke. We therefore performed an analysis from the individual patient data from 11 randomized clinical trials of CABG versus PCI to compare procedural and long-term rates of stroke and the impact of stroke on survival.

METHODS

STUDY SELECTION AND DATA COLLECTION. Details of this pooled analysis have been previously published (5). In summary, a systematic search was performed on July 19, 2017, to identify randomized clinical trials comparing CABG with PCI for the treatment of multivessel or LM disease. Studies were selected if: 1) patients were randomly assigned to undergo CABG or PCI treatment; 2) patients had multivessel or LM disease; 3) patients did not present with an acute myocardial infarction; 4) PCI was performed using stents (BMS or DES) and not balloon angioplasty; 5) the occurrence of stroke was collected beyond 30 days of follow-up; and 6) >1-year follow-up for all-cause mortality was available. The study was performed according to PRISMA (Preferred Reporting Items for Systematic Review and MetaAnalyses) guidelines (6).

Investigators from 11 individual trials provided the data for the current pooled analysis: ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease) (7), ARTS (Arterial Revascularization Therapy Study) (8), MASS II (Medicine, Angioplasty, or Surgery Study) (9), SoS (Stent or Surgery) trial (10), SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (11), PRECOMBAT (Bypass Surgery Versus Angioplasty Using SirolimusEluting Stent in Patients With Left Main Coronary Artery Disease) trial (12), FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial (13), VA CARDS (Coronary Artery Revascularization in Diabetes) (14), BEST (Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) (15), EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (16), and NOBLE (Percutaneous Coronary Angioplasty Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis) trial (17) (Supplemental Figure 1). Only the data from the LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial (n = 105) could not be obtained (18). Baseline and procedural characteristics of individual trials are presented in Supplemental Table 1. Local medical ethics committees approved each trial at the time of study execution. Patients in each of the 11 trials provided written informed consent.

OUTCOMES, DEFINITIONS, AND FOLLOW-UP. Follow-up time was calculated from the time of the procedure to allow a universal definition of follow-up among trials. Follow-up time was calculated from randomization if patients experienced a stroke or died before the procedure took place or if patients did not undergo revascularization but only received medical treatment. The primary endpoint of this study was stroke. A procedural stroke was defined as stroke occurring in the first 30 days after the procedure. All trials, except the SoS trial, collected stroke during the entire duration of follow-up; the SoS trial collected stroke only up to 1 year after revascularization (10). Stroke was defined using the criteria applied in each study and consisted mainly of: 1) a focal neurological deficit of central origin lasting >24 h with or without confirmation with neuroimaging; or 2) a deficit lasting >72 h without the need for confirmation with neuroimaging. Secondary endpoints of the present study were all-cause mortality after stroke and a composite of all-cause mortality or stroke. In all trials, a clinical events committee adjudicated the events.

Patients with MVD were defined as having 2or 3vessel disease without LM disease. Patients with LM disease were defined as having LM disease, either isolated or in combination with single-vessel disease or MVD.

STATISTICAL ANALYSIS. The main analyses were performed according to the intention-to-treat principle. Outcome data were also analyzed on an as-treated basis to determine more accurately the impact of the specific procedure on stroke rate. Continuous variables are expressed as a mean ± SD and compared using Student's *t*-tests, and discrete data are presented as frequencies and compared using chi-square tests. We pooled the individual patient data from 11 trials to provide descriptive statistics and unadjusted Kaplan-Meier curves. Hazard ratios (HR) of CABG versus PCI for stroke were estimated using random effects Cox proportional hazards models that were stratified by trial, using a gamma frailty term to account for heterogeneity among trials. Frailties are unobserved factors, distributed as g random variables with a mean of 1 and variance w. Hence, the variance of the frailty terms represents heterogeneity in baseline risk among trials. The statistical significance of the variance parameter was assessed using the likelihood ratio test. The rate of stroke was estimated at 30 days and 5 years, and landmark analyses were performed after 30 days follow-up to assess the long-term risk of stroke after CABG versus PCI. Prespecified subgroup analyses of 30-day and 5-year stroke rates were performed according to baseline clinical and anatomical characteristics and multivessel or LM disease. The p values for interaction were calculated in the random effects Cox proportional hazards models. Due to a limited number of events in several of the subgroup analyses of 30-day stroke, no frailty model could be built; in these specific analyses, the HR and interaction terms were analyzed through standard Cox proportional hazards models. We did not perform interaction analyses on stratification according to LM/MVD, because the LM and MVD groups are not mutually exclusive. Moreover, we explored the impact of off-pump CABG as opposed to on-pump CABG among trials that provided information on the use of cardiopulmonary bypass, the impact of PCI being performed with BMS or DES, and the impact of single versus dual antiplatelet therapy (DAPT) at hospital discharge on stroke. Multivariable Cox proportional hazards models that included baseline and procedural characteristics were constructed to predict 30-day and 5year stroke. Variables were included in the multivariable model if $p < 0.15$ at univariable analyses, with the variable CABG versus PCI being forced into the model. The impact of stroke within 30 days of the procedure on mortality was explored using the Kaplan-Meier method comparing patients with and without 30-day stroke. The composite rate of all cause mortality or stroke was explored at 30 days and 5 years in the overall group of patients, and according to status of diabetes, SYNTAX score tertiles, and MVD or LM disease. Two-sided $p < 0.05$ was considered

to indicate statistical significance. Statistical analyses were performed using SPSS software version 21 (IBM Corporation, Armonk, New York) or R software version 3.2.4 (Institute for Statistics and Mathematics of Wirtschaftsuniversität, Wien, Austria).

Table 1. Baseline, Procedural, and Discharge Data of Randomized Cohorts.

	PCI (n = 5,753)	CABG (n = 5,765)
Age, yrs	63.6 ± 9.8 (5,753)	63.7 ± 9.9 (5,765)
Female	23.9 (1,373/5,753)	23.8 (1,371/5,765)
BMI >30 kg/m^2	28.1 (1,548/5,506)	28.3 (1,558/5,511)
Smoking, current	22.3 (1,274/5,701)	22.3 (1,273/5,703)
Diabetes	38.5 (2,215/5,753)	37.7 (2,171/5,765)
Insulin treatment	12.9 (545/4,234)	11.9 (504/4,245)
Hypertension	67.6 (3,880/5,739)	68.1 (3,913/5,748)
Hypercholesterolemia	69.5 (3,982/5,726)	67.3 (3,862/5,735)
Peripheral vascular disease	8.2 (424/5,158)	8.5 (440/5,164)
Carotid artery disease	7.8 (161/2,072)	8.1 (168/2,074)
Previous TIA or CVA	5.4 (218/4,052)	6.2 (253/4,054)
Previous MI	28.0 (1,438/5,138)	27.5 (1,417/5,156)
LV dysfunction, <30%	0.9 (49/5,303)	1.0 (54/5,430)
Unstable disease	34.6 (1,786/5,158)	34.2 (1,767/5,160)
3-vessel disease*	58.6 (2,460/4,201)	61.8 (2,594/4,197)
Left main disease	38.8 (2,233/5,753)	38.9 (2,245/5,765)
SYNTAX score	26.0 ± 9.3 (4,081)	26.0 ± 9.8 (4,057)
PCI–DES used†	73.4 (4,120/5,610)	—
PCI–number of stents	3.1 ± 2.0 (4,935)	—
CABG–LIMA use	—	96.2 (4,574/4,753)
CABG–BIMA use	—	18.7 (771/4,122)
CABG–off-pump	—	27.5 (1,085/3,945)
Aspirin at discharge	97.3 (4,487/4,612)	95.5 (3,814/3,994)
Thienopyridine at discharge	96.7 (4,479/4,630)	45.1 (1,815/4,026)
DAPT at discharge	95.1 (4,384/4,612)	44.0 (1,759/3,994)

Values are mean ± SD (N) or % (n/N). *Of the group of patients with multivessel disease. †Data only for patients who were randomized to PCI and indeed underwent PCI. The type of stent used was not available for 1 patient enrolled in the VA CARDS trial. BIMA, bilateral internal mammary artery; BMI, body mass index; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DES, drugeluting stents; LIMA, left internal mammary artery; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA, transitory ischemic attack; VA CARDS, Coronary Artery Revascularization in Diabetes.

ROLE OF THE FUNDING SOURCE. Whereas several of the individual studies were funded by industry, this collaborative analysis had no external funding and did not involve any of the original study sponsors.

RESULTS

STUDY POPULATION. Eleven trials randomized 11,518 patients; 5,765 patients were randomly assigned to CABG and 5,753 to PCI. Of the 5,765 patients assigned to CABG, 5,421 underwent CABG (94%), 233 underwent PCI (4%), and 111 underwent neither procedure (2%). Of the 5,753 patients assigned to PCI, 5,610 underwent PCI (98%), 101 underwent CABG (2%), and 42 underwent neither procedure (1%). In the as-treated analysis, 5,522 patients underwent CABG and 5,843 patients underwent PCI. Data on crossovers in each study are presented in Supplemental Table 2.

Patient enrollment was between 1995 and 2015 (Supplemental Table 1). PCI was performed in 4 trials exclusively with BMS (MASS II, ERACI II, SoS, and ARTS; n = 1,518 PCI patients), in 3 trials with firstgeneration DES (PRECOMBAT, SYNTAX, and FREEDOM; n = 2,156 PCI patients), in 3 trials with second-generation DES (BEST, EXCEL, and NOBLE; n = 1,978 PCI patients), and in 1 trial with a mix of stent generations (VA CARDS; n = 101 PCI patients).

There were no clinically significant differences in baseline characteristics between patients randomly assigned to either CABG or PCI (Table 1). The pooled patient population had a mean age of 63.6 ± 9.8 years, and 24% were female. Diabetes was present in 38% of patients, with 12% on insulin. LM disease was present in 39% of patients. At discharge, antiplatelet therapy was prescribed significantly more often after PCI than after CABG ($p < 0.001$ for all analyses). The mean follow-up was 3.8 ± 1.4 years.

FREQUENCY AND PREDICTORS OF STROKE. A total of 293 strokes occurred during follow-up. The cumulative stroke rate at 5-year follow-up was 2.6% (129 strokes) in patients randomized to PCI and 3.2% (164 strokes) in patients randomized to CABG (HR: 0.77; 95% confidence interval (CI): 0.61 to 0.97; $p = 0.027$) (Central Illustration, panel A). At 30 days, stroke occurred in 21 patients (0.4%) randomized to PCI and 64 patients (1.1%) randomized to CABG (HR: 0.33; 95% CI: 0.20 to 0.53; $p < 0.001$) (Central Illustration, panel B). The rate of stroke between 31 days up to 5 years was comparable between PCI (2.2%; 108 strokes)

and CABG (2.1%; 100 strokes) (HR: 1.05; 95% CI: 0.80 to 1.38; p = 0.72) (Central Illustration, panel B). Results were similar in the as-treated analysis. The value of the frailty parameter theta (q) for heterogeneity was q = 0.09 (p < 0.001). In a multivariable analysis, the only independent predictor of 30-day stroke was CABG (HR: 8.33; 95% CI: 1.06 to 62.5; p = 0.043). In multivariable analysis of 5-year stroke, CABG was not an independent predictor (HR: 1.43; 95% CI: 0.94 to 2.13; p = 0.089). In 7 trials that provided data on on-pump or offpump CABG (n = 3,945), 28% of patients underwent off-pump CABG surgery. Rates of stroke at 30 days were 0.6% (6 of 1,085) after off-pump CABG and 1.4% (40 of 2,860) after on-pump CABG (p = 0.13), with 5-year rates of 2.9% (25 of 1,085) versus 3.5% (84 of 2,860), respectively (p = 0.60). After CABG, 44% of patients were discharged on DAPT. The rate of stroke at 5 years was comparable between patients on DAPT or single antiplatelet therapy (3.1% (48 of 1,759) vs. 3.8% (67 of 2,109), respectively; p = 0.84).

Whether PCI was performed with BMS or DES did not have an impact on the rate of stroke at 30 days (0.5% (7 of 1,518) vs. 0.3% (14 of 4,235); p = 0.89) or 5 years (2.6% (39 of 1,518) vs. 2.7% (90 of 4,235); p = 0.83). When analyzing BMS and DES trials separately, the difference between PCI and CABG in 5-year stroke was similar among trials that used exclusively BMS (2.6% vs. 3.2%, respectively; p = 0.39) or DES (2.7% vs. 3.3%, respectively; p = 0.038) (p for interaction = 0.78). Only 190 patients were discharged on single antiplatelet therapy after PCI, with the rates of stroke at 5 years being 2.5% (91 of 4,384) for patients on DAPT and 4.0% (5 of 190) for patients on single antiplatelet therapy (p = 0.41).

SUBGROUP ANALYSES. There were no significant interactions between any the treatment effects of PCI versus CABG in the rate of stroke at 30 days except for the presence of hypercholesterolemia (p for interaction = 0.023) (Figure 1). There were no significant interactions between PCI and CABG and baseline characteristics on the rate of stroke at 5 years, except for diabetes (Figures 2 and 3). As shown in Figure 3A, the 5-year rate of stroke was lower in patients with diabetes randomized to PCI versus CABG (2.6% (n = 47 of 2,215) vs. 4.9% (n = 86 of 2,171), respectively; HR: 0.52; 95% CI: 0.37 to 0.75; p < 0.001) but not in patients without diabetes (2.6% (n = 82 of 3,538) vs. 2.4% (n = 78 of 3,594), respectively; HR: 1.04; 95% CI: 0.77 to 1.42; p = 0.78) (p for interaction = 0.004).

In 4,478 randomized patients with LM disease, treatment with PCI compared with CABG resulted in a lower rate of stroke at 30 days (0.3% (6 of 2,233) vs. 1.0% (23 of 2,245), respectively; HR: 0.26; 95% CI: 0.11 to 0.64; p = 0.003), a difference that was no longer present at 5 years (2.6% (43 of 2,233) vs. 2.6% (51 of 2,245), respectively; HR:

0.83; 95% CI: 0.55 to 1.24; p = 0.36) (Figure 3B). In 7,040 randomized patients with

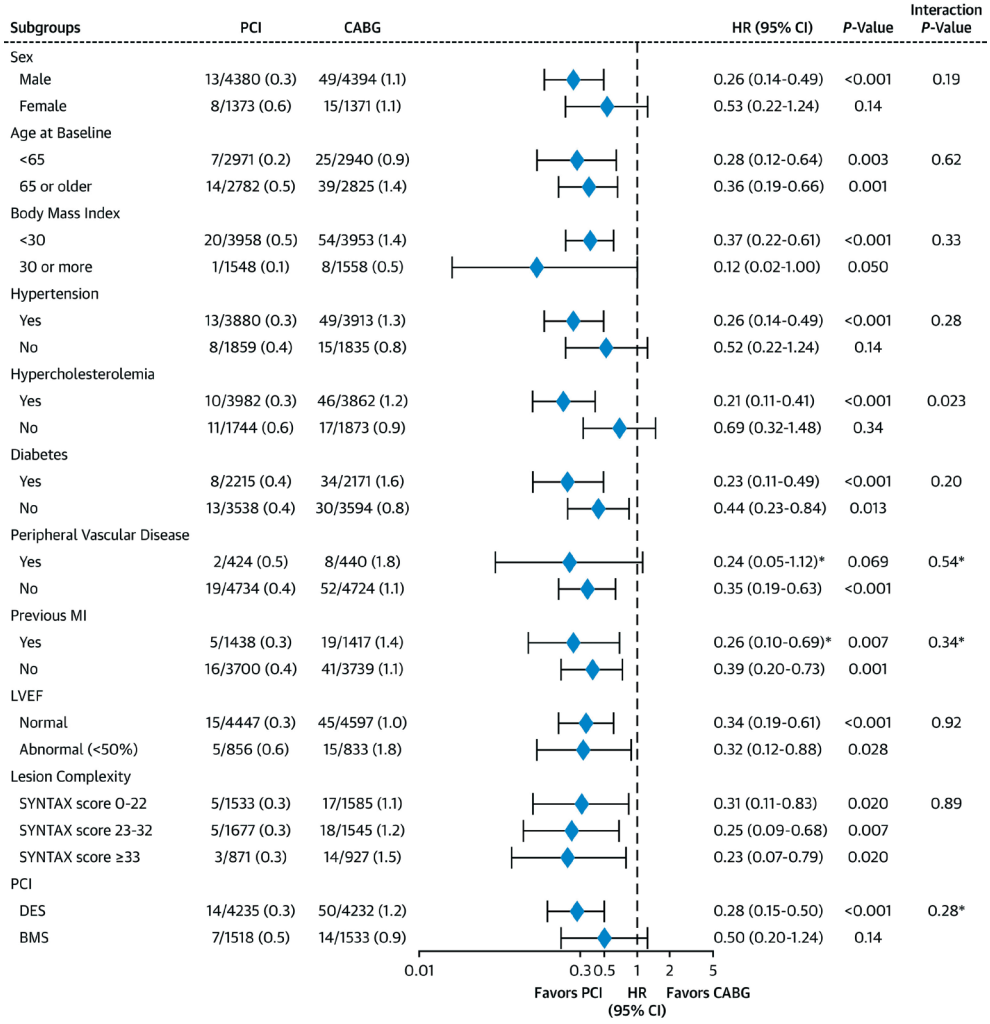


Figure 1. Stroke After PCI Versus CABG at 30 Days in Subgroup Analyses According to Baseline and Procedural Characteristics. *Due to the low number of events, the interaction term was derived from Cox proportional hazards models and not the random effects Cox proportional hazards models that included a frailty term. BMS, bare-metal stents; CI, confidence interval; DES, drug-eluting stents; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

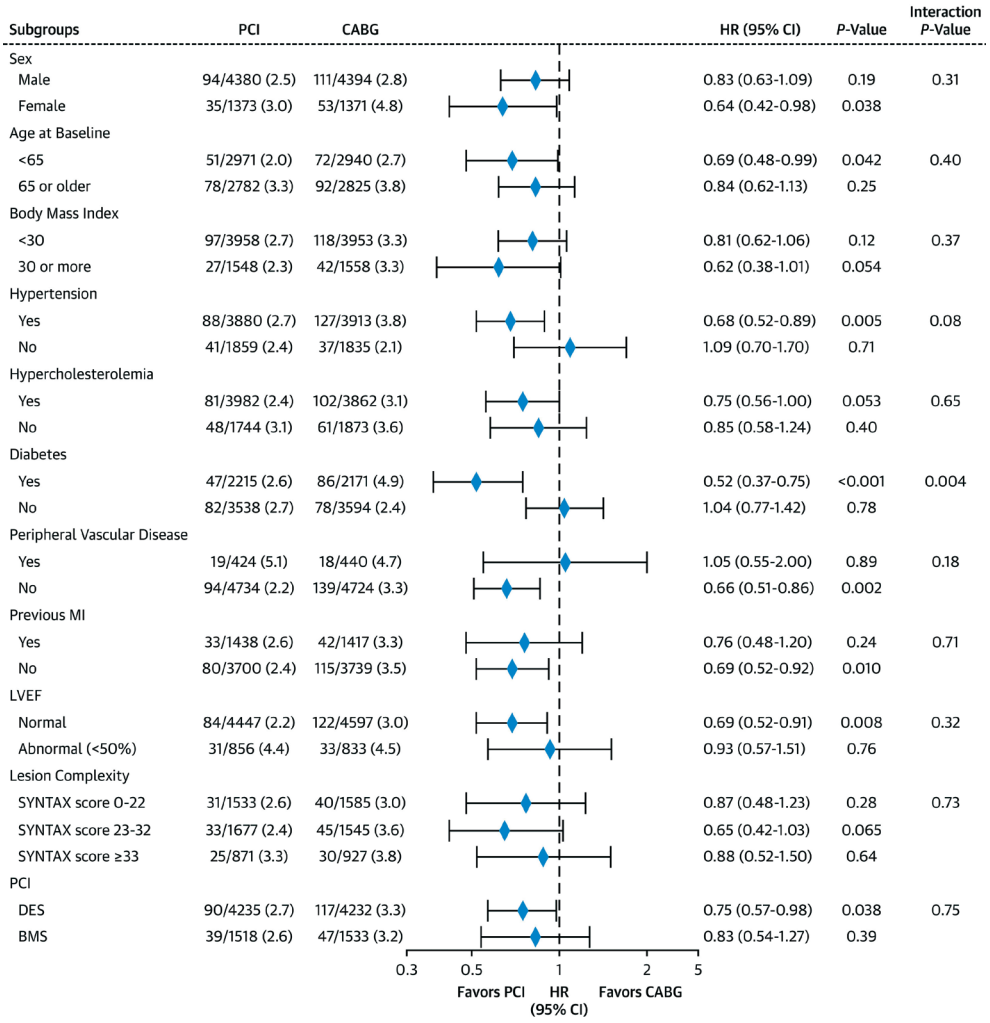


Figure 2. Stroke After PCI Versus CABG During 5-Year Follow-Up in Subgroup Analyses According to Baseline and Procedural Characteristics. Abbreviations as in Figure 1.

MVD, the rate of stroke was significantly lower after PCI than after CABG at 30 days (0.4% (15 of 3,520) vs. 1.2% (41 of 3,520), respectively; HR: 0.36; 95% CI: 0.20 to 0.65; p < 0.001) and 5 years (2.7% (86 of 3,520) vs. 3.6% (n = 113 of 3,520), respectively; HR: 0.74; 95% CI: 0.56 to 0.99; p = 0.039).

IMPACT OF STROKE ON MORTALITY. A total of 976 deaths occurred during follow-up. Patients who experienced a stroke within 30 days after revascularization had significantly higher 5-year mortality compared with patients who did not experience a stroke within 30 days after both CABG (41.5% (23 of 64) vs. 8.9% (414 of 5,701); p < 0.001) and after PCI (45.7% (9 of 21) vs. 11.1% (530 of 5,732), respectively; p < 0.001) (Figure 4).

COMPOSITE ENDPOINT OF ALL-CAUSE MORTALITY OR STROKE. As shown in Table 2, the rate of all-cause mortality or stroke at 30 days was 1.6% (91 of 5,753) after PCI versus 2.4% (135 of 5,765) after CABG (p = 0.003). The composite of all-cause mortality or stroke between 31 days and 5 years was higher after PCI compared with CABG (11.6% vs. 9.3%, respectively; HR: 1.26; 95% CI: 1.11 to 1.32; p < 0.001). Finally, the overall difference in the composite of all-cause mortality or stroke after PCI versus CABG at 5 years did not reach statistical significance (13.0% vs. 11.4%, respectively; HR: 1.11; 95% CI: 0.99 to 1.24; p = 0.069).

Although there were no significant interactions, the benefit of CABG over PCI was generally seen in patients with diabetes and higher SYNTAX scores. The difference between PCI and CABG in rates of the composite of all-cause death or stroke at 30 days was similar in patients with MVD (1.8% (n = 62) vs. 2.6% (n = 90); HR: 0.68; 95% CI: 0.49 to 0.94; p = 0.020) and LM disease (1.3% (n = 29) vs. 2.0% (n = 45); HR: 0.64; 95% CI: 0.40 to 1.02; p = 0.062).

Between 31 days and 5 years, the rate of the composite of all-cause death or stroke after PCI versus CABG was 11.9% (n = 371) versus 9.1% (n = 274) in patients with MVD (HR: 1.31; 95% CI: 1.12 to 1.53; p < 0.001) and 11.3% (n = 174) versus 10.2% (n = 147) in patients with LM disease (HR: 1.16; 95% CI: 0.93 to 1.44; p = 0.20). At 5 years, there was a difference between PCI and CABG in patients with MVD (13.5% (n = 433) vs. 11.4% (n = 364); HR: 1.16; 95% CI: 1.01 to 1.33; p = 0.041) but not in patients with LM disease (12.4% (n = 203) vs. 12.0% (n = 192); HR: 1.02; 95% CI: 0.84 to 1.25; p = 0.81).

Table 2. Composite Endpoint of All-Cause Mortality or Stroke.

	30 Days				31 Days–5 Years				5 Years			
	PCI vs. CABG	HR (95% CI)	p Value	Interaction p Value	PCI vs. CABG	HR (95% CI)	p Value	Interaction p Value	PCI vs. CABG	5 Years HR (95% CI)	p Value	Interaction p Value
All	1.6 (91) vs. 2.4 (135)	0.67 (0.51–0.87)	0.003	—	11.6 (545) vs. 9.3 (421)	1.26 (1.11–1.43)	<0.001	—	13.0 (636) vs. 11.4 (556)	1.11 (0.99–1.24)	0.069	—
Diabetes												
Yes	2.2 (48) vs. 3.1 (66)	0.70 (0.48–1.02)	0.063	0.68	15.4 (263) vs. 11.2 (180)	1.39 (1.15–1.68)	<0.001	0.14	17.2 (311) vs. 13.9 (246)	1.20 (1.02–1.42)	0.031	0.19
No	1.2 (43) vs. 1.9 (69)	0.63 (0.43–0.92)	0.016		9.5 (282) vs. 8.3 (241)	1.15 (0.97–1.37)	0.11		10.6 (325) vs. 10.0 (310)	1.03 (0.88–1.21)	0.69	
SYNTAX score												
0–22	0.9 (14) vs. 2.2 (34)	0.42 (0.23–0.79)	0.007	0.15	10.3 (116) vs. 8.0 (94)	1.19 (0.91–1.57)	0.20	0.22	11.1 (130) vs. 10.0 (128)	0.98 (0.77–1.26)	0.89	0.09
23–32	1.4 (23) vs. 2.1 (32)	0.65 (0.38–1.12)	0.12		12.8 (162) vs. 11.4 (123)	1.18 (0.93–1.49)	0.16		14.0 (185) vs. 13.3 (155)	1.07 (0.86–1.32)	0.56	
$33	2.6 (23) vs. 2.7 (25)	0.97 (0.55–1.71)	0.92		16.3 (111) vs. 11.1 (75)	1.61 (1.20–2.16)	0.001		18.5 (134) vs. 13.6 (100)	1.45 (1.12–1.88)	0.005	

Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses expressed as % (n). CI, confidence interval; HR, hazard ratio; other abbreviations as in Table 1.

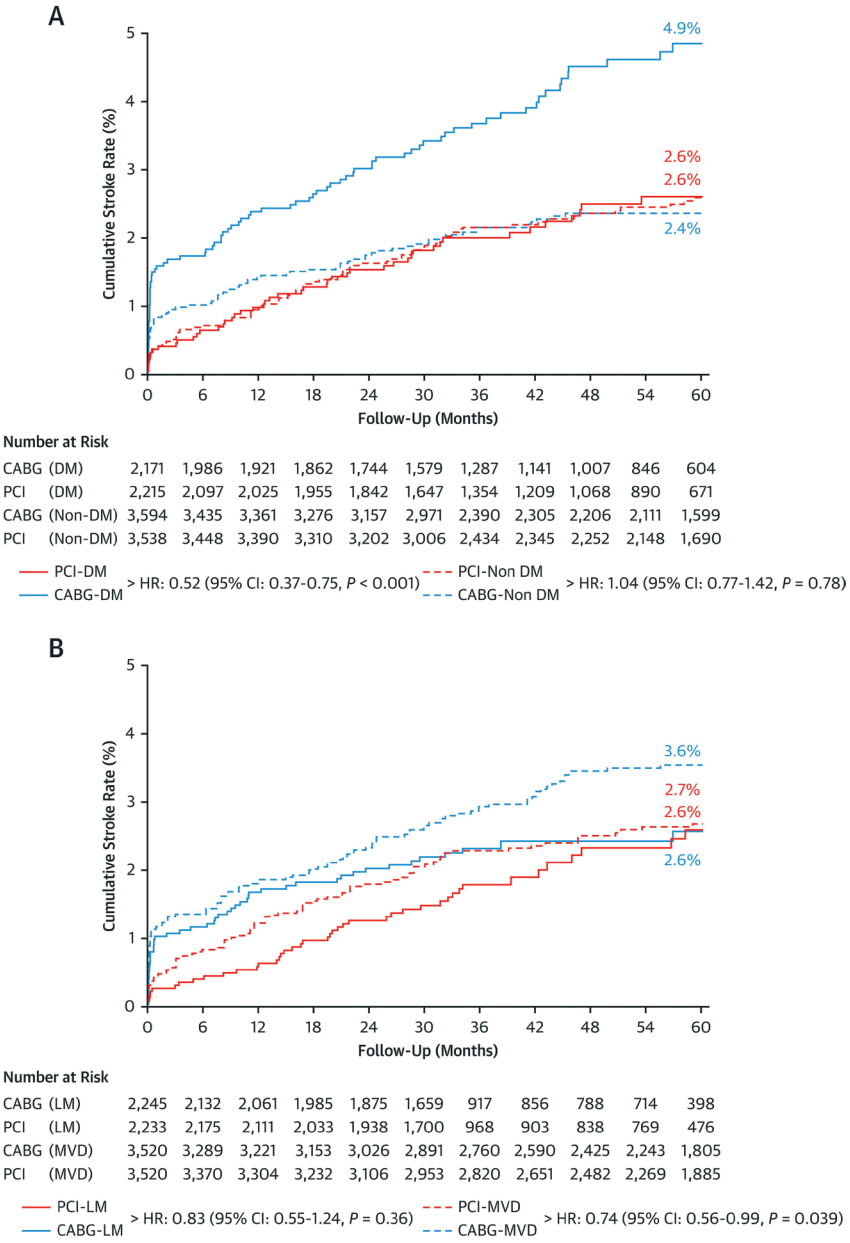


Figure 3. Stroke After PCI Versus CABG During 5-Year Follow-Up of Patients With and Without DM, LM, or MVD. Stroke after PCI (percutaneous coronary intervention) versus CABG (coronary artery bypass grafting) during 5-year follow-up of patients with and without diabetes mellitus (DM) **(A)** and patients with left main (LM) or multivessel disease (MVD) **(B)**. There was significant diabetes-by-treatment interaction (p for interaction = 0.004). No interaction was explored for LM and MVD, because these groups are not mutually exclusive. Abbreviations as in Figure 1.

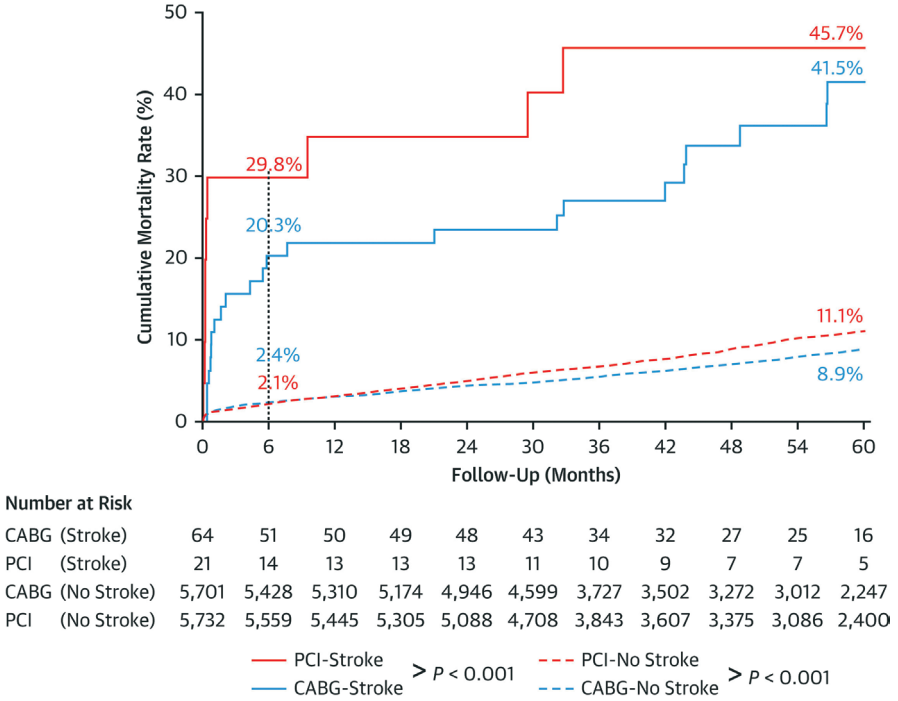


Figure 4. Mortality After PCI Versus CABG of Patients With and Without Stroke Within 30 Days After Revascularization. Solid lines indicate patients who experienced a stroke within the first 30 days of follow-up, and dotted lines indicate patients without a stroke. Follow-up starts at 30 days, indicated here as time 0. Abbreviations as in Figures 1 and 3.

DISCUSSION

In this individual patient-data pooled analysis based on 11 randomized clinical trials comparing CABG with PCI for multivessel or LM disease, CABG resulted in significantly higher rates of 5-year stroke. A higher rate of stroke in the first 30 days after the procedure drove the difference. Rates of stroke between 31-day and 5-year follow-ups were similar between CABG and PCI. The increased 5-year risk of stroke with CABG compared with PCI was confined to patients with MVD and diabetes. Strokes occurring within 30 days after the procedure were strongly associated with increased long-term mortality, with a rate approaching 50% at 5 years. The composite of allcause mortality or stroke was lower after PCI compared with CABG at 30 days, but higher after PCI at 5 years, especially in patients with diabetes, MVD, and in those with high SYNTAX scores.

Periprocedural strokes are more common after CABG, with an absolute incremental risk of nearly 0.7% observed in the present large-scale study. The mechanisms underlying the increased risk of stroke with surgery are likely multifactorial. First, most CABG procedures are performed on-pump with cannulation and clamping of the aorta; even if they are performed off-pump, the aorta is often manipulated for construction of the proximal anastomosis (19–21). Data from cohort studies suggests that limiting, if not completely avoiding, aortic manipulation by performing an anaortic off-pump CABG procedure reduces stroke rates substantially (22,23). The use of bilateral internal mammary arteries avoids the need for proximal anastomoses and side-clamping of the aorta and has been associated with lower stroke rates (24). In the current study, the rate of bilateral internal mammary arteries use was relatively low. Second, strategies to reduce post-operative bleeding that are often required after CABG (but not after PCI), such as usage of tranexamic acid, lead to a hypercoagulable state that may increase the risk of stroke (25). Third, post-operative atrial fibrillation is frequent after CABG and increases the risk of stroke in the early post-operative period (26,27). Fourth, periods of hypoperfusion during surgery and early postoperative low cardiac output syndrome may impair brain perfusion, leading to ischemia and watershed strokes (28). Another hypothesis is that strokes may be lower after PCI due to the routine use of DAPT after stent implantation (29). However, in the current study, we did not find this to be associated with a lower rate of stroke after CABG.

Our landmark analysis demonstrated a low rate of stroke beyond 30 days that was similar between CABG and PCI. The need for more repeat revascularizations after PCI than after CABG, as shown in these individual trials (30), did not result in a higher stroke rate during follow-up after PCI. Moreover, subgroup analyses demonstrated no significant heterogeneity according to baseline characteristics, with the important exception of diabetes: stroke rates were nearly doubled after CABG compared with PCI in patients with diabetes, but nearly identical in patients without diabetes (p for interaction = 0.004). This finding should be considered hypothesis-generating and requires confirmation in future studies.

Whereas PCI was associated with lower periprocedural rates of stroke compared with CABG in patients with MVD and patients with LM disease, the long-term risk of stroke was higher after PCI than CABG in those with LM disease. This finding is likely the result of inclusion of the NOBLE trial in which long-term rates of strokes were inexplicably higher after PCI than after CABG (17), a finding not confirmed in any other randomized trial.

When the endpoints of all-cause mortality and stroke were combined in a composite endpoint, there was no significant difference in the 5-year rates of death or stroke between PCI and CABG. However, CABG was associated with superior outcomes in patients with MVD, diabetes, and higher SYNTAX scores, but not in patients with LM disease.

It remains unclear whether there is a difference in the severity of stroke occurring after CABG and PCI. In the FREEDOM trial, severely disabling strokes accounted for 55% of all strokes after CABG but only 27% of all strokes after PCI (13). An indepth analysis of strokes occurring in the SYNTAX trial showed that residual defects were present at discharge in 68% of patients after CABG and in 47% after PCI (31). It is evident that quality of life of patients who experienced a stroke is impaired, although no studies have compared quality of life of patients experiencing a stroke after CABG or PCI to determine whether the higher rate of residual deficits after CABG is translated into significantly lower long-term quality of life. We did, however, find that 5-year mortality was markedly higher among patients who experienced a 30-day stroke versus those who did not experience a stroke, regardless of whether stroke occurred after CABG or PCI.

The present analysis has several strengths. Sharing of trial data among investigators is crucial to compare low-frequency outcomes such as stroke and to assess safety and efficacy in patient subgroups (32). This collaborative analysis from 11 randomized clinical trials had sufficient power to analyze the occurrence of stroke after CABG versus PCI. Moreover, the inclusion of patients from different geographic areas increases the external validity of our results. All trials prospectively enrolled patients and had a clinical events com mittee to adjudicate events, confirming the diagnosis of stroke.

STUDY LIMITATIONS. First, techniques for both CABG and PCI have evolved during the patient inclusion period that ranged from 1995 to 2015. Although we showed consistent stroke rates after PCI with BMS and DES and for off-pump and onpump CABG, it is unclear whether other unmea sured factors may have played a role. Second, there was some heterogeneity in baseline characteristics between trials, with more recent trials enrolling patients with more complex coronary artery disease and with a greater frequency of diabetes. Third, several variables potentially related to stroke after CABG were not collected in many of the included trials (e.g., aortic manipulation, post-operative atrial fibrillation), and therefore our multivariable models could not include factors that may have predicted periprocedural stroke. Fourth, rates of stroke may have been underestimated

because independent neurological evaluation was not routinely performed nor required for the diagnosis of stroke. Involvement of a stroke neurologist has been shown to increase the number of strokes found after aortic valve procedures and is now mandatory in trials of transcatheter and surgical aortic valve replacement (33). Fifth, data on the severity of stroke and residual deficits after stroke could not be evaluated because only 2 trials collected such data and definitions varied. Finally, antiplatelet therapy may reduce the occurrence of stroke, but we lacked data of medication regimens during follow-up. Nevertheless, most patients receive at least 1 antiplatelet agent after CABG or PCI, which is generally considered to be sufficient for stroke prevention.

CONCLUSIONS

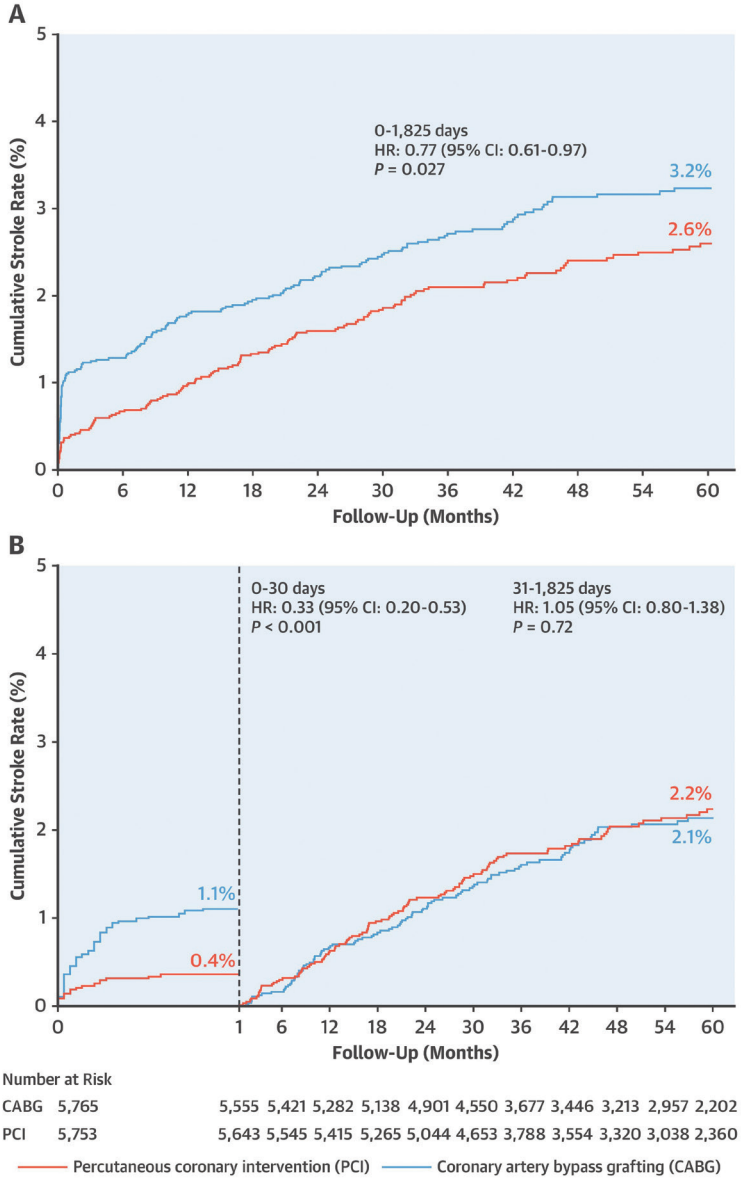
In this large-scale, individual patient-data pooled analysis of randomized trials including patients with multivessel or LM coronary artery disease who underwent coronary revascularization, PCI resulted in significantly lower 30-day and 5-year rates of stroke than CABG, with similar rates of stroke between 31 days and 5 years. The increased 5-year risk of stroke with CABG was confined to patients with MVD and diabetes. Five-year mortality was high in patients experiencing a stroke within 30 days after both CABG and PCI. The differential risks of stroke after PCI and CABG should be considered in the comprehensive assessment of the long-term risk-benefit ratio of these alternative revascularization options.

CLINICAL PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing coronary revascularization for multivessel or LM disease, rates of stroke were lower after PCI than CABG during the first 30 days but comparable thereafter during the next 5 years.

TRANSLATIONAL OUTLOOK: More studies are needed on strategies to prevent perioperative stroke in patients undergoing CABG surgery.

Central illustration Stroke After Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting.



This figure illustrates the comparison of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) on stroke during 5-year follow-up **(A)** and in landmark analyses of stroke at 30 days and beyond 30 days **(B)**. Hazard ratios (HR) are for PCI versus CABG. CI, confidence interval.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline and procedural characteristics in individual trials.

Characteristic	ERACI-II (n = 450)	ARTS (n = 1205)	MASS-II (n = 408)	SoS (n = 988)	SYNTAX (n = 1800)	PRECOMBAT (n = 600)	FREEDOM (n = 1900)	VA CARDS (n = 198)	BEST (n = 880)	NOBLE (n = 1184)	EXCEL (n = 1905)
Patient inclusion	1996-1998	1997-1998	1995-2000	1996-1999	2005-2007	2004-2009	2005-2010	2006-2010	2008-2013	2008-2015	2010-2014
Study location	Argentina	Europe, South America, Australasia	Brazil	Europe, Canada	Europe, US	Korea	North America, South America, Europe, India, Australasia	US	Asia	Europe	North America, South America, Europe, India, Australasia
Age	60.7 ± 10.2	60.6 ± 10.8	59.8 ± 9.0	61.4 ± 9.3	65.1 ± 9.7	62.2 ± 9.7	62.1 ± 9.1	62.4 ± 7.2	64.5 ± 9.4	66.2 ± 9.7	65.9 ± 9.6
Female sex	21% (93/450)	23% (283/1205)	31% (125/408)	21% (206/988)	22% (402/1800)	24% (141/600)	29% (544/1900)	1% (2/198)	29% (251/880)	22% (256/1184)	23% (441/1905)
BMI >30 kg/m^2	NA	22% (260/1203)	25% (100/408)	22% (220/982)	32% (579/1799)	3% (20/595)	42% (789/1896)	68% (132/195)	4% (35/880)	29% (336/1155)	34% (639/1904)
Smoking current	52% (233/540)	27% (323/1203)	33% (134/408)	15% (149/988)	21% (363/1760)	29% (172/600)	16% (298/1900)	25% (48/195)	20% (177/880)	20% (235/1170)	22% (415/1850)
Diabetes	17% (78/450)	17% (208/1205)	28% (115/408)	14% (142/988)	25% (452/1800)	32% (192/600)	100% (1900/1900)	100% (198/198)	41% (363/880)	15% (184/1184)	29% (554/1905)
Insulin treatment	NA	NA	5% (20/408)	3% (28/988)	10% (182/1800)	3% (19/600)	32% (615/1900)	NA	4% (38/880)	NA	8% (147/1905)
Hypertension	71% (318/450)	45% (540/1205)	62% (253/408)	45% (447/988)	75% (1349/1787)	53% (317/600)	85% (1612/1900)	96% (187/195)	67% (591/880)	66% (775/1182)	74% (1404/1892)
Hyperlipidemia	61% (275/450)	58% (694/1201)	73% (298/408)	52% (509/988)	78% (1391/1785)	41% (247/600)	84% (1592/1900)	58% (111/191)	52% (461/880)	80% (946/1183)	70% (1320/1875)
Peripheral vascular disease	23% (103/450)	5% (64/1205)	0% (0/408)	7% (66/988)	10% (177/1800)	4% (22/600)	10% (197/1900)	14% (27/195)	3% (27/880)	NA	9% (181/1896)
Carotid artery disease	6% (25/450)	NA	NA	NA	8% (148/1800)	NA	NA	NA	NA	NA	8% (156/1896)
Previous TIA/stroke	2% (10/450)	NA	NA	4% (37/988)	8% (150/1788)	NA	3% (65/1900)	10% (20/198)	8% (70/879)	NA	6% (119/1903)
Previous MI	28% (126/450)	43% (520/1205)	47% (191/408)	45% (448/988)	33% (585/1780)	6% (33/567)	26% (487/1900)	42% (81/195)	6% (54/880)	NA	17% (330/1888)
LV dysfunction (<30%)	0% (0/446)	0% (0/1121)	0% (0/408)	1% (4/771)	2% (34/1800)	1% (5/542)	1% (27/1900)	7% (12/177)	1% (5/744)	1% (5/1020)	1% (11/1804)
Unstable disease	92% (412/450)	36% (438/1205)	0% (0/408)	0% (0/988)	29% (513/1800)	45% (272/600)	31% (584/1900)	NA	44% (384/880)	17% (206/1183)	39% (744/1892)
Number of lesions	2.6 ± 0.6	2.8 ± 1.0	2.8 ± 0.8	2.8 ± 1.1	4.0 ± 1.7	3.0 ± 1.0	NA	3.6 ± 1.5	3.4 ± 1.2	1.7 ± 1.0	NA
Three-vessel disease	49% (220/450)	33% (403/1205)	58% (238/408)	42% (419/988)	61% (1095/1800)	51% (308/600)	83.4% (1573/1887)	66% (120/181)	77% (679/880)	NA	NA

Left main disease	5% (21/450)	0.1% (1/1205)	0% (0/408)	1% (7/988)	39% (705/1800)	100% (600/600)	0.4% (8/1900)	0% (0/198)	5% (47/880)	100% (1184/1184)	100% (1905/1905)
SYNTAX score	NA	NA	NA	NA	28.7 ± 11.4	25.1 ± 10.0	26.2 ± 8.6	NA	24.8 ± 7.7	22.4 ± 7.3	26.5 ± 9.3
PCI – DES used	0% (0/222)	0% (0/593)	0% (0/205)	0% (0/488)	100% (885/885)	100% (276/276)	100% (939/939)	100% (93/93)	100% (413/413)	100% (580/580)	100% (935/935)
PCI – number of stents	1.4 ± 0.6	NA	1.2 ± 0.9	2.6 ± 1.4	4.6 ± 2.3	2.7 ± 1.4	4.1 ± 1.9	NA	3.4 ± 1.4	2.2 ± 1.2	2.4 ± 1.5
CABG – LIMA use	95% (198/209)	NA	95% (188/198)	93% (450/485)	97% (827/854)	94% (233/248)	94% (843/893)	NA	100% (382/382)	96% (545/565)	99% (908/923)
CABG – BIMA use	0.5% (1/209)	NA	32% (65/203)	10% (50/485)	28% (236/854)	NA	12% (110/893)	NA	NA	8% (44/549)	29% (265/923)
CABG – off-pump	NA	NA	NA	NA	15% (128/854)	63% (155/248)	18% (165/893)	32% (26/82)	66% (252/382)	16% (88/564)	29% (271/923)
Complete revascularization	68% (303/448)	82% (992/1205)	57% (224/408)	70% (693/988)	60% (1043/1741)	69% (416/600)	90% (1701/1900)	NA	61% (518/855)	94% (543/577)*	NA
Aspirin at discharge	100% (450/450)	NA	98% (391/397)	NA	92% (1633/1766)	99% (593/600)	98% (1826/1867)	98% (172/176)	97% (852/880)	93% (539/580)*	98% (1823/1867)
Thienopyridine at discharge	53% (238/450)	NA	48% (194/408)	NA	59% (1037/1766)	94% (565/600)	62% (1158/1867)	55% (96/176)	93% (818/880)	97% (566/580)*	66% (1227/1867)
DAPT at discharge	53% (238/450)	NA	47% (187/397)	NA	56% (987/1766)	93% (560/600)	81% (1513/1867)	54% (94/176)	92% (806/880)	92% (532/580)*	65% (1204/1867)
Mean follow, years	4.7 ± 1.1	4.8 ± 0.9	4.5 ± 1.3	4.7 ± 0.9	4.4 ± 1.4	4.7 ± 1.0	3.5 ± 1.4	1.4 ± 0.9	4.0 ± 1.3	3.2 ± 1.5	2.6 ± 0.7

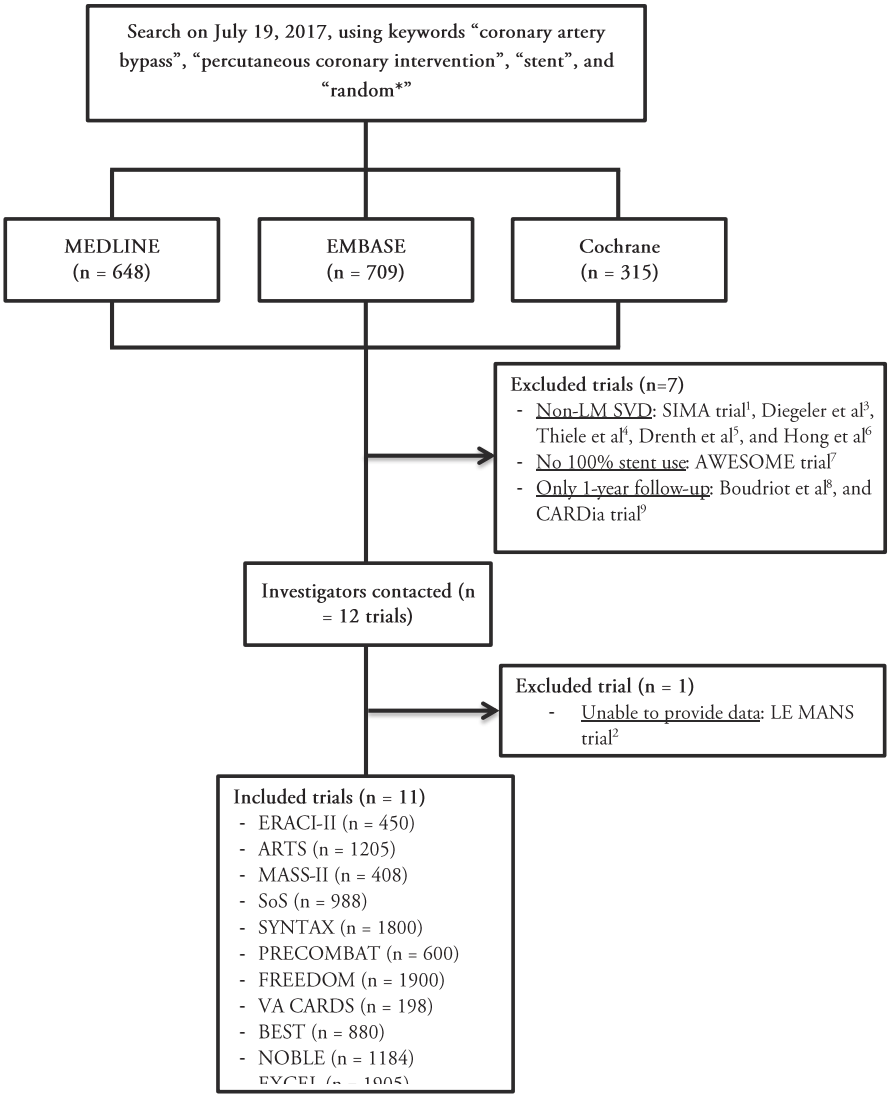
Values are present as mean ± SD or n/N (%). NA, not available; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug-eluting stents; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; DAPT, dual antiplatelet therapy.

Supplemental Table 2. Data on cross-overs in each trial.

	Randomized to CABG			Randomized to PCI		
	Actual CABG	Actual PCI	No Revasc.	Actual CABG	Actual PCI	No Revasc.
ARTS	579	19	7	6	593	1
ERACI-II	209	16	0	3	222	0
MASS-II	198	0	5	6	194	5
VA-CARDS	81	11	5	6	93	2
SoS	487	11	2	7	480	1
FREEDOM	893	18	36	5	939	9
SYNTAX	854	16	27	11	885	7
PRECOMBAT	248	51	1	24	276	0
BEST	382	51	9	19	413	6
NOBLE	567	23	2	7	580	5
EXCEL	923	17	17	7	935	6

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Supplemental Figure 1. Study selection flow-chart.



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Chapter 9

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

Milojevic M, Kappetein AP, Head SJ.

N Engl J Med. 2017;376:1892.

TO THE EDITOR:

Myles et al. found that treatment with tranexamic acid in patients undergoing coronary-artery surgery showed benefits over placebo by lowering the risk of major hemorrhage or cardiac tamponade leading to reoperation. Tranexamic acid was associated with higher rates of seizures than placebo but with similar rates of death and thrombotic events at 30 days. The trial was designed to use tranexamic acid at a loading dose of 12.5 mg per kilogram, a maintenance infusion of 6.5 mg per kilogram per hour, and a dose of 1 mg per kilogram added to the cardiopulmonary-bypass priming solution (1). However, a fixed dose of 100 mg per kilogram was used and was lowered to 50 mg per kilogram after the enrollment of 30% of the trial population.

On the basis of other evidence (2), patients who received 50mg per kilogram were probablyless effectively treated without evidence of better safety (3). In the trial, the low dose of tranexamic acid was not safer than the high dose in terms of the risk of seizure (0.7% vs. 0.6%) but was associated with significantly lower efficacy in terms of bloodloss (P=0.03 for interaction)and number of units transfused (P=0.02 for interaction). Moreover, plasma concentrations of tranexamic acid were aimed to be effective for 6 to 8 hours, but no target concentrations or intraoperative measurements of concentrations are mentioned. For clinicians who want to administer tranexamic acid routinely, the trial is unclear about which dose is to be used. We believe that the evidence supports a high dose overa low dose.

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Chapter 10

Incidence, Characteristics, Predictors, and Outcomes of Repeat Revascularization After Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting: The SYNTAX Trial at 5 Years

Parasca CA, Head SJ, **Milojevic M**, Mack MJ, Serruys PW, Morice MC, Mohr FW, Feldman TE, Colombo A, Dawkins KD, Holmes DR Jr, Kappetein AP.

JACC Cardiovasc Interv. 2016;9:2493-2507.

ABSTRACT

OBJECTIVES: The study sought to determine the incidence, predictors, characteristics, and outcomes of repeat revascularization during 5-year follow-up of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial.

BACKGROUND: Limited in-depth long-term data on repeat revascularization are available from randomized trials comparing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

METHODS: Incidence and timing of repeat revascularization and its relation to the long-term composite safety endpoint of death, stroke, and myocardial infarction were analyzed in the SYNTAX trial (n = 1,800) using Kaplan-Meier analysis.

RESULTS: At 5 years, repeat revascularization occurred more often after initial PCI than after initial CABG (25.9% vs. 13.7%, respectively; $p < 0.001$), and more often consisted of multiple repeat revascularizations (9.0% vs. 2.8%, respectively; $p = 0.022$). Significantly more repeat PCI procedures were performed on de novo lesions in patients after initial PCI than initial CABG (33.3% vs. 13.4%, respectively; $p < 0.001$). At 5-year follow-up, patients who underwent repeat revascularization versus patients not undergoing repeat revascularization had significantly higher rates of the composite safety endpoint of death, stroke, and myocardial infarction after initial PCI (33.8% vs. 16.6%, respectively; $p < 0.001$), and a trend was found after initial CABG (22.4% vs. 15.8%, respectively; $p = 0.07$). After multivariate adjustment, repeat revascularization was an independent predictor of the composite safety endpoint after both initial PCI (hazard ratio (HR): 2.2; 95% confidence interval (CI): 1.6 to 3.0; $p < 0.001$) and initial CABG (HR: 1.8; 95% CI: 1.2 to 2.9; $p = 0.011$).

CONCLUSIONS: Repeat revascularization rates are significantly higher after initial PCI than after initial CABG for complex coronary disease. Repeat revascularization is an independent predictor of death, stroke, and myocardial infarction for myocardial revascularization.

INTRODUCTION

Repeat revascularization is a controversial endpoint in clinical trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG). It is often criticized because of its subjective and biased nature, as the underlying incentive to perform repeat revascularization may be different after PCI than CABG.

However, repeat revascularization as an outcome can be of great importance (1,2). Although it is usually considered an adverse outcome or failure of the initial treatment, repeat revascularization is an efficient therapy associated with a reduction in morbidity and mortality (3,4). Although its incidence is highly time dependent, the need for repeat revascularization also varies greatly depending on the studied population (5,6).

Few data beyond early follow-up of repeat revascularization exist and therefore it remains largely unclear which patients are at risk for repeat revascularization, what current practice regarding repeat revascularization does entail, and what is the actual impact of repeat revascularization on short-term and long-term clinical outcomes. Particularly, despite the completion of numerous trials comparing PCI with CABG, very limited in-depth long-term follow-up data on practice of repeat revascularization in randomized trials is available (1,7). Therefore, this study aims to provide insights from a randomized trial comparing PCI with CABG into the predictors, characteristics, and short-term and 5-year outcomes of repeat revascularization in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial.

METHODS

STUDY DESIGN. The SYNTAX trial is a randomized, prospective, multicenter trial on the basis of an allcomers design that included patients with complex coronary artery disease as defined by the presence of unprotected left main or 3-vessel disease. Patients (n = 1,800) were randomized on a 1:1 basis by the Heart Team consensus to undergo either CABG or PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific, Marlborough, Massachusetts). If considered unsuitable for randomization, patients were entered in to 1 of 2 parallel nested registries (PCI registry, n = 193; CABG registry, n = 1,077) (8). This study only included comparisons between the randomized cohorts of patients. Indications for repeat

revascularization were not specified in the original trial protocol and were on the basis of local practice at each participating site.

DEFINITIONS. The primary endpoint of the SYNTAX trial was a composite of major adverse cardiac or cerebrovascular events that includes all-cause death, myocardial infarction (MI), stroke, and repeat revascularization. Because the primary interest of this analysis is to investigate repeat revascularization and clinical outcomes during follow-up, the individual endpoints of repeat revascularization (all, repeat PCI, and repeat CABG) and all-cause mortality were evaluated, as well as the composite safety endpoint of all-cause death, MI, and stroke. Definitions of these individual components have been previously reported (9). An independent Clinical Events Committee, including cardiologists, cardiac surgeons, and a neurologist, reviewed all primary clinical endpoints. In addition, revascularization was divided into target vessel revascularization (TVR), target vessel target lesion revascularization (TLR), revascularization of a de novo lesion in a target vessel (remote TVR), revascularization of a de novo lesion in a nontarget vessel (NTVR), de novo lesion revascularization (in both target and nontarget vessel), and, for patients who had previously undergone CABG, revascularization of a bypass graft.

During the Heart Team meeting when patients were assessed for randomization, both the interventional cardiologist and surgeon documented which vessels with a >1.5 mm diameter and a 50% stenosis needed revascularization. Incomplete revascularization was assessed by correlating this pre-operative statement to the actual revascularization.

Throughout the manuscript, initial PCI and initial CABG will refer to the procedures to which patients were randomized at the start of the SYNTAX trial. Repeat PCI and repeat CABG will refer to repeat revascularizations, irrespective of what was the initial procedure.

As initial therapy after randomization, a staged revascularization procedure was allowed if performed within 72 h after the first procedure and during the same hospital stay or within 14 days in patients with renal insufficiency or post-procedural contrastinduced nephropathy. All staged procedures have been adjudicated by the Clinical Events Committee as such.

To determine procedural adverse events of repeat revascularization, the following events were counted when occurring during 30 days after repeat

revascularization: death, stroke, subsequent repeat revascularization(s) and MI, and the corresponding composite endpoint. To evaluate the effect of successful repeat revascularization, an additional analysis was performed by not taking into account MI events occurring on the same day as the repeat revascularization. Furthermore, a comparative analysis between groups of initial PCI and initial CABG was performed of elective and urgent repeat revascularizations.

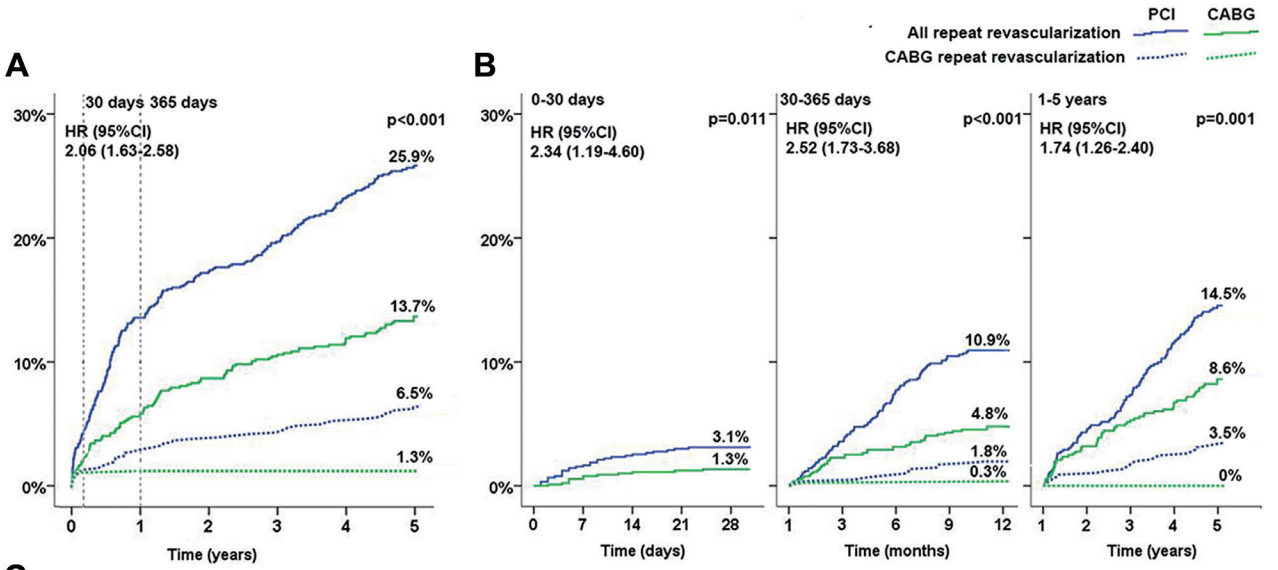
Indications leading to repeat revascularization included stable angina, unstable angina, MI, silent ischemia (established by stress testing), and other reasons including both periprocedural complications (bleeding, graft failure or stent thrombosis, and technique-related adverse events) and evidence of progression of disease (not classified as angina).

STATISTICAL METHODS. Continuous variables are given as mean ± SD and compared using the Student *t* test. Discrete variables are expressed as counts and percentages, and comparisons between groups were done with the chi-square or Fisher exact test, when appropriate. For comparisons across subgroups, the Kruskal-Wallis test, the Wilcoxon rank sum test using pairwise comparisons, and the chi-square test for comparing proportions (of categorical variables) between >2 groups have been used. Bonferroni method was used to adjust p values for multiple comparisons. Five-year clinical outcomes were estimated using the Kaplan-Meier method, with comparisons made using the log-rank test (overall or pairwise as appropriate). To account for the informative censoring in the presence of multiple endpoints, competing risks survival analysis was performed by means of nonparametric methods using the cumulative incidence competing risk method (10–12). Landmark analyses were used to describe the occurrence of repeat revascularization in time: early (within 30 days), intermediate (between 30 days and 1 year), or late (through 1 to 5 years). After careful selection of baseline characteristics and periprocedural variables on the basis of clinical judgment (Supplemental Appendix), univariable assessment and multiple testing to ensure stability, a multivariable model has been fitted. Multivariable predictors of repeat revascularization after initial PCI and initial CABG were determined using Backward Wald stepwise selection with a significance level of <0.10 for entry and exit in a Cox proportional hazards model. Correlations between variables were explored with the Pearson correlation coefficient and highly correlated variables were not included in the multivariable model. To evaluate the impact of repeat revascularization on clinical outcomes, a comparison was made between patients with no repeat revascularization versus events that occurred after repeat revascularization in patients who did undergo repeat revascularization.

Multivariable Cox proportional hazard analyses were used to determine whether repeat revascularization was an independent predictor of the composite safety endpoint of all-cause death, stroke, and MI (Model 1), while adjusting for baseline characteristics and periprocedural variables (Supplemental Appendix). A second model was fitted to relate the type of repeat revascularization (repeat PCI revascularization and repeat CABG revascularization) with the composite safety endpoint, using a stepwise 2-block model (Model 2). A third model was fitted to relate target lesion revascularization (restenosis surrogate) and de novo lesion revascularization (marker of disease progression) with the composite safety endpoint, using a stepwise 2-block model (Model 3). The proportionality of hazards assumption was checked using the global proportionality of hazards test on the basis of Schoenfeld residuals. There was no departure from the proportionality of hazards assumption in the groups of patients with initial CABG (predictors of repeat revascularization: chi-square = 9.11, df = 10, p = 0.52; predictors of composite safety endpoint: chi-square = 5.35, df = 9, p = 0.80) and initial PCI (predictors of repeat revascularization: chi-square = 13.66, df = 9, p = 0.14; predictors of composite safety endpoint: chi-square = 6.34, df = 8, p = 0.61). A 2-sided p value of 0.05 was considered to be statistically significant for all tests. All analyses were conducted using SPSS 21.0 (SPSS Inc., Chicago, Illinois) and SAS V.9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

INCIDENCE, TIMING, AND TYPE OF REPEAT REVASCULARIZATION. During 5-year follow-up, 459 repeat revascularization events were registered; 86.2% consisting of repeat PCI and 14.8% of repeat CABG revascularization. Rates of repeat revascularization at 5 years after initial CABG and initial PCI were 13.7% and 25.9%, respectively ($p < 0.001$). At all time points during follow-up, repeat revascularization rates were significantly higher after initial PCI than after initial CABG (Figure 1). After initial CABG treatment, almost all repeat CABG procedures were performed within 30 days, with other repeat revascularizations thereafter consisting almost exclusively of repeat PCI. Conversely, after initial PCI treatment, the relative number of subsequent CABG procedures in relation to repeat PCI revascularization remained stable over the length of follow-up. Patients after initial PCI more often required multiple repeat revascularizations (9.0% vs. 2.8%, respectively; p = 0.022) (Figure 2).



C

	5-year			0-30 days			31-365 days			1 -5 years		
	PCI group	CABG group	p-value	PCI group	CABG group	p-value	PCI group	CABG group	p-value	PCI group	CABG group	p-value
All repeat revascularization	25.9%	13.7%	<0.001	3.1%	1.3%	0.011	10.9%	4.8%	<0.001	14.5%	8.6%	0.001
PCI repeat revascularization	21.5%	12.9%	<0.001	2.5%	0.5%	0.001	9.1%	4.1%	<0.001	11.6%	8.6%	0.062
CABG repeat revascularization	6.5%	1.3%	<0.001	1.0%	0.9%	0.94	1.8%	0.3%	0.003	3.5%	0%	<0.001

Figure1. Incidence of Repeat Revascularization. (A) All-time and **(B)** landmark Kaplan-Meier estimates of repeat revascularization with separation of events **(C)**. Solid lines indicate any repeat revascularizations whereas dotted lines indicate repeat CABG procedures after initial PCI (blue lines) or CABG (green lines). The p values are by log-rank. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

Kaplan-Meier analysis revealed a higher 5-year cumulative incidence of TVR, mainly driven by TLR (19.0% after initial PCI vs. 8.4% after initial CABG; p < 0.001), but no difference between groups in remote-TVR or NTVR (Figure 3). There were no differences in revascularization for de novo lesions between initial PCI and initial CABG (4.8% vs. 6.4%, respectively; p = 0.14). The 5-year cumulative incidence of stent thrombosis or graft occlusion was similar after initial PCI and initial CABG (5.5% and 4.0%, respectively; p = 0.13), as well as the rate of stent thrombosis or graft occlusion leading to repeat revascularization (4.1% and 3.2%, respectively; p = 0.31).

In a competing risks analysis, the cumulative incidence of repeat revascularization was 19.7% after initial PCI and 11.6% after initial CABG (Supplemental Appendix). After initial PCI, death and MI as a first event occurred at a rate of 8.1% and 8.2%, respectively. After initial CABG, death and MI occurred as a first event at a rate of 9.2% and 3.7%, respectively.

Although considered as a single index procedure and not as repeat revascularization, 13.6% patients in the initial PCI group underwent a planned staged revascularization, resulting in a higher number of actual procedures for some patients in the initial PCI group.

REASONS FOR REPEAT REVASCULARIZATION. Symptomatic angina pectoris was the primary indication for repeat PCI and its occurrence was largely similar among patients randomized to initial PCI versus initial CABG (Table 1). The percentage of repeat PCI procedures that were TVR were the majority of all repeat PCI procedures after both initial PCI and initial CABG (89.6% and 83.0%, respectively; p = 0.125), and about one-half of repeat PCIs in both initial PCI and initial CABG groups were performed as TLR procedures (55.7% vs. 51.5%, respectively; p = 1.00). Significantly more repeat PCIs were performed on de novo lesions in patients randomized to initial PCI versus those randomized to initial CABG (33.3% vs. 13.4%, respectively; p < 0.001). About 18% of repeat PCIs in patients initially treated with CABG were performed in bypass grafts.

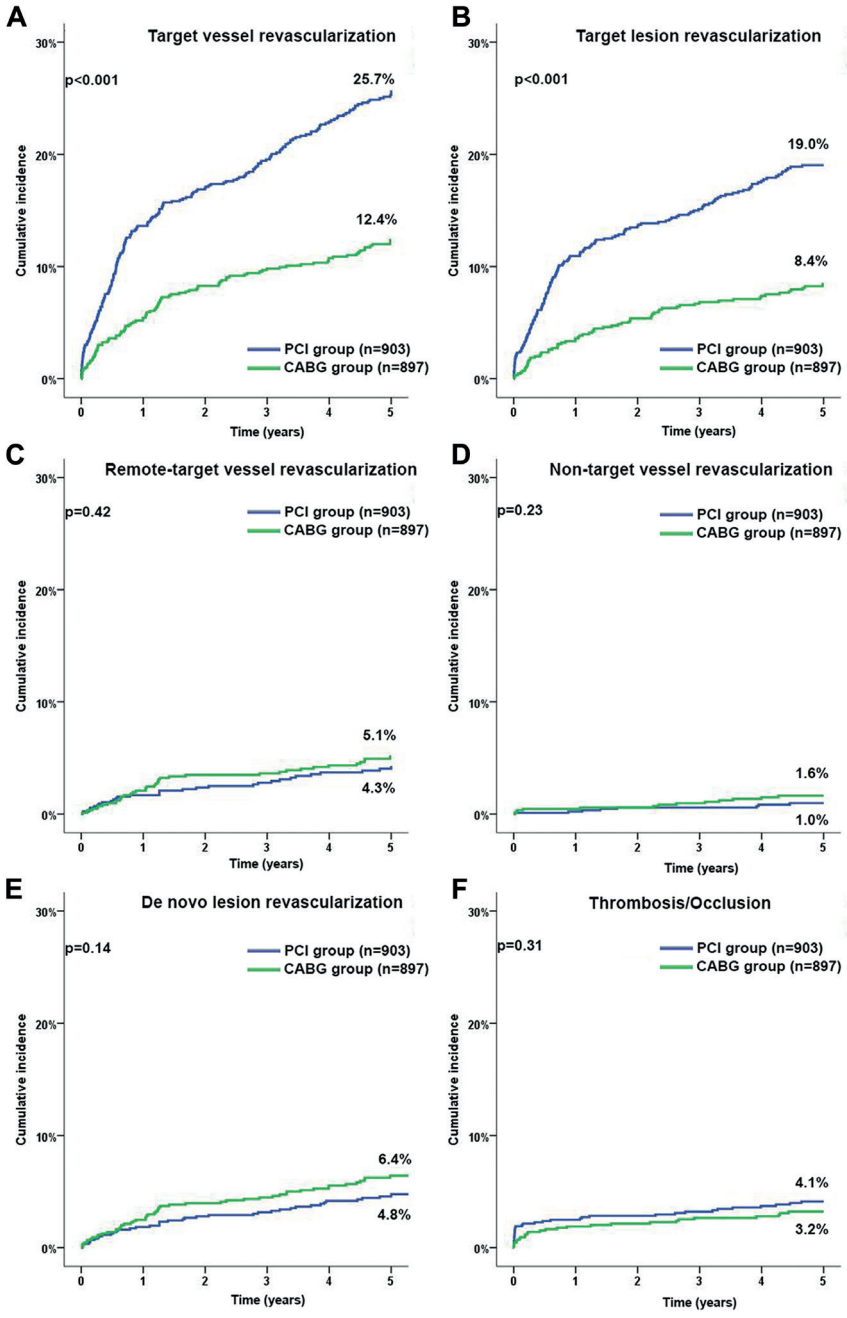


Figure 3. Repeat Revascularization During 5-Year Follow-Up. Cumulative incidence of **(A)** target vessel revascularization, **(B)** target lesion revascularization, **(C)** remote target vessel revascularization, **(D)** nontarget vessel revascularization, **(E)** de novo lesion revascularization, and **(F)** thrombosis or occlusion leading to repeat revascularization.
Abbreviations as in Figure 1.

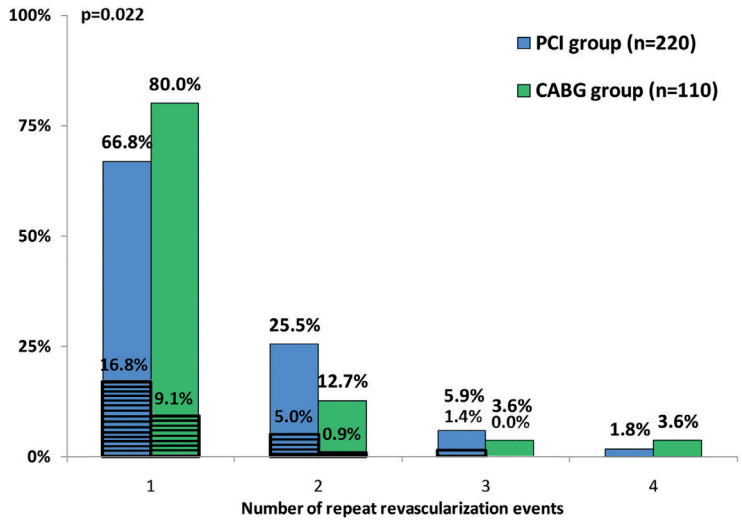


Figure 2. Number and Type of Repeat Revascularizations. Proportion of patients requiring repeat revascularization after PCI (blue) and CABG (green). Of the entire 1,800 patients, more patients after initial PCI than after initial CABG required multiple repeat revascularizations (9.0% vs. 2.8%, respectively; p = 0.022). Hashed rectangles represent repeat CABG revascularizations. Abbreviations as in Figure 1.

After initial PCI treatment, 54 patients underwent repeat CABG, of which 88.9% had symptoms of angina. In about 70% the indication for repeat CABG was stable or unstable angina, whereas in only 5.6% this was because of acute MI. At the time of repeat CABG during follow-up, 64.8% of patients initially treated with PCI required reintervention in 3 vessels (vs. 12.5% after initial CABG; p = 0.021), whereas patients initially treated with CABG predominantly required reintervention in 1 vessel at the time of repeat CABG (62.5% vs. 18.5% after initial PCI; p = 0.048). Target vessel repeat revascularization by repeat CABG was similar in both groups (PCI: 85.9%, CABG: 83.3%; p = 1.00), whereas TLR was higher in patients initially treated with PCI. In the initial CABG group, few repeat CABG procedures were preceded by symptoms of angina or acute MI, but 4 events (50%) were as a result of acute complications within days of the initial CABG procedure (hemorrhage or acute graft failure) (Table 1).

BASELINE AND PROCEDURAL CHARACTERISTICS BY REPEAT REVASCULARIZATION. In the initial PCI group, patients that required repeat revascularization, compared with those who did not, had a significantly higher rate of diabetes, particularly medically treated diabetes (34.1% vs. 22.8%, respectively; p < 0.001), and had more complex disease

Table 1. Characteristics of Repeat Revascularizations at the Time of Repeat Revascularization.

	Repeat CABG Revascularization				All Repeat PCI Revascularizations			
	PCI Group (n = 54 Procedures)	CABG Group (n = 8 Procedures)	p Value		PCI Group (n = 259 Procedures)	CABG Group (n = 133 Procedures)	p Value	
			Unadjusted	Adjusted			Unadjusted	Adjusted
Angina symptoms								
Yes	88.9 (48/54)	37.5 (3/8)	0.003	0.009	74.1 (192/259)	76.7 (102/133)	0.58	1.00
No	5.6 (3/54)	37.5 (3/8)	0.024	0.072	16.2 (42/259)	17.3 (23/133)	0.79	1.00
Silent ischemia	5.6 (3/54)	25.0 (2/8)	0.12	0.36	9.3 (24/259)	6.0 (8/133)	0.33	0.99
Indication leading to revascularization								
Stable angina	42.6 (23/54)	12.5 (1/8)	0.14	0.70	35.5 (92/259)	40.6 (54/133)	0.33	0.413
Unstable angina	27.8 (15/54)	25.0 (2/8)	1.00	1.00	25.1 (65/259)	21.8 (29/133)	0.47	0.47
Acute MI	5.6 (3/54)	0 (0/8)	1.00	1.00	16.2 (42/259)	9.8 (13/133)	0.08	0.20
Silent ischemia	5.6 (3/54)	12.5 (1/8)	0.43	1.00	10.0 (26/259)	6.8 (9/133)	0.28	0.413
Other	18.5 (10/54)	50.0 (4/8)	0.07	0.35	13.1 (34/259)	21.8 (28/133)	0.042	0.20
Vessel type†								
Target vessel	85.9 (122/142)	83.3 (10/12)	0.68	1.00	89.6 (336/375)	83.0 (161/194)	0.025	0.125
Bypass graft	0 (0/142)	75.0 (9/12)	<0.001	<0.001	0.5 (2/375)	18.0 (35/194)	<0.001	<0.001
Target lesion	64.1 (91/142)	8.3 (1/12)	<0.001	<0.001	55.7 (209/375)	51.5 (100/194)	0.34	1.00
De novo lesion	21.8 (31/142)	0 (0/12)	0.13	0.65	33.3 (125/375)	13.4 (26/194)	<0.001	<0.001
Nontarget vessel‡								
De novo lesion	14.1 (20/142)	8.3 (1/12)	1.00	1.00	10.4 (39/375)	14.9 (29/194)	0.11	0.55
Number of vessels revascularized								
1	18.5 (10/54)	62.5 (5/8)	0.016	0.048	45.9 (84/183)	53.9 (55/102)	0.22	0.66
2	16.7 (9/54)	25.0 (2/8)	0.62	1.00	30.1 (55/183)	24.5 (25/102)	0.34	1.00
3	64.8 (35/54)	12.5 (1/8)	0.007	0.021	24.0 (44/183)	21.6 (22/102)	0.66	1.00

Values are % (n/N). *Bonferroni correction method for multiple comparisons. †Considered on a vessel basis and not a patient basis for repeat coronary artery bypass grafting (CABG) (percutaneous coronary intervention (PCI): 142 vessels revascularized during 54 events in 54 patients, CABG: 12 vessels revascularized during 8 events in 8 patients) and all repeat PCIs (PCI: 375 vessels revascularized during 259 events in 183 patients, CABG 194 vessels revascularized during 133 events in 102 patients). ‡All de novo lesions. MI, myocardial infarction.

as described by the SYNTAX score (26.6 ± vs. 24.7 ± 11.6, respectively; p = 0.023) at the time of randomization (Table 2). They had more stents implanted but had a higher rate of incomplete revascularization (53.6% vs. 39.9% among patients not requiring repeat revascularization; p < 0.001).

In the initial CABG group, patients requiring repeat revascularization were younger, more often underwent an emergent index procedure, and had a lower mean logistic European System for Cardiac Operative Risk Evaluation score (3.0 ± 2.8 vs. 4.0 ± 4.6, respectively; p = 0.001) at the time of randomization (Table 2). The complexity of disease was comparable between patients requiring repeat revascularization and those who did not, as was the rate of incomplete revascularization (36.1% vs. 43.3%, respectively; p = 0.24). The number of grafts was similar, but patients who underwent repeat revascularization more frequently underwent complete arterial revascularization, particularly with the use of a radial artery.

PREDICTORS OF REPEAT REVASCULARIZATION. Tables with univariable analyses are provided in the Supplemental Appendix. In the final multivariable model to predict repeat revascularization in the initial PCI group, medically treated diabetes was a strong independent predictor of repeat revascularization (hazard ratio (HR): 1.59; 95% confidence interval (CI): 1.20 to 2.12; p = 0.001) (Table 3). The complexity of coronary disease as described by the SYNTAX score failed to be a predictor, but instead the number of overlapping stents (HR: 1.34; 95% CI: 1.09 to 1.64; p = 0.005) and incomplete initial revascularization (HR: 1.54; 95% CI: 1.17 to 2.02; p = 0.002) were found to be independent predictors of repeat revascularization. Repeat revascularization was also related to lack of antiplatelet therapy as medication at discharge.

In the initial CABG group, enrollment in the United States (HR: 1.75; 95% CI: 1.09 to 2.81; p = 0.020) and off-pump CABG (HR: 1.51; 95% CI: 0.94 to 2.44; p = 0.091) were predictors of repeat revascularization (Table 3). The presence of a left coronary artery lesion was found protective for repeat revascularization (HR: 0.55; 95% CI: 0.32 to 0.94; p = 0.028). Use of statins but lack of acetylsalicylic acid at discharge appears to be inversely related to repeat revascularization.

PROCEDURAL EVENTS FOLLOWING REPEAT REVASCULARIZATION. Thirty-day adverse event rates following any repeat revascularization were higher after initial PCI than after initial CABG; the composite endpoint of death, subsequent repeat revascularization, and MI occurred in 22.7% and 11.8%, respectively (p = 0.017) (Table 4). No strokes were registered in the interval of 30-days following any repeat revascularization. MI events occurring on the same day as repeat revascularization were excluded to assess the impact of successful repeat

revascularization on the 30-day adverse event rates. Under these circumstances the difference between initial PCI and initial CABG lost statistical significance (13.6% vs. 9.1%, respectively; p = 0.23). Differences between initial PCI and initial CABG groups were consistent among all repeat revascularization and PCI repeat revascularization.

Although 30-day adverse event rates occurring after elective repeat revascularization were almost identical between groups, there was a trend toward a higher rate of the composite endpoint after urgent repeat revascularization in the PCI group (35.8% vs. 22.2% in the CABG group; p = 0.096), mainly driven by the MI rate (26.0% vs. 6.7% in the CABG group; p = 0.006).

OUTCOMES AT 5-YEAR FOLLOW-UP. After initial PCI, the composite safety endpoint of all-cause death, stroke and MI was significantly higher among patients that underwent repeat revascularization as compared to those who did not (27.9% vs. 16.6%, respectively; p < 0.001) (Figure 4). After initial CABG there was no difference in the composite safety endpoint (14.9% vs. 15.8%, respectively; p = 0.62).

Among patients that underwent repeat revascularization, patients that underwent initial PCI versus initial CABG had significantly higher rates of the composite of death, MI, or subsequent repeat revascularization (57.4% vs. 38.4%, respectively; p = 0.003), which was primarily driven by significantly higher rates of subsequent repeat revascularization (43.4% vs. 25.3%, respectively; p = 0.012) and MI (19.2% vs. 4.8%, respectively; p = 0.001). There was no significant difference in mortality in patients who underwent repeat revascularization after initial PCI versus initial CABG (20.2% vs. 13.9%, respectively; p = 0.095) (Figure 5A). When considering only patients that underwent repeat PCI procedures, not only subsequent repeat revascularization and MI, but also 5-year mortality was higher in patients after initial PCI (20.6% vs. 11.5% after initial CABG; p = 0.021) (Figure 5B). Conversely, the composite safety endpoint was similar after initial PCI and initial CABG in patients not undergoing any repeat revascularization (HR: 0.96; 95% CI: 0.74 to 1.24; p = 0.73).

Outcome of MI may be masked by the fact that repeat revascularization is sometimes performed because of an MI, whereas MI can also occur periprocedurally as a result of repeat revascularization. Rates of an MI before repeat revascularization were similar after initial PCI and initial CABG (1.7% vs. 1.2%, respectively; p = 0.42), as well as rates of MI without any repeat revascularization

(3.4% vs. 2.4%, respectively; p = 0.19). Rates of repeat revascularization without any MI during 5-year follow-up were significantly higher after initial PCI than after initial CABG (19.2% vs. 11.9%, respectively; p < 0.001). In the initial PCI group as compared to the initial CABG group, an MI occurred significantly more often on the same day as repeat revascularization (3.3% vs. 0.4%, respectively; p < 0.001). An MI also occurred significantly more often after repeat revascularization in the initial PCI versus initial CABG group (1.0% vs. 0.1%, respectively; p = 0.022).

THE INDEPENDENT IMPACT OF REPEAT REVASCULARIZATION. After performing multivariable analyses (Supplemental Appendix), adjustment for baseline and periprocedural characteristics identified repeat revascularization as an independent predictor of the composite safety endpoint in the initial PCI group (HR: 1.65; 95% CI: 1.20 to 2.27; p = 0.002) (Table 5), for both repeat PCI (HR: 1.67; 95% CI: 1.20 to 2.32; p = 0.002) and repeat CABG (HR: 1.72; 95% CI: 1.02 to 2.88; p = 0.041). Target lesion revascularization was also identified as an independent predictor of the composite safety endpoint (HR: 1.69; 95% CI: 1.20 to 2.38; p = 0.003), but not de novo lesion revascularization (HR: 1.49; 95% CI: 0.80 to 2.79; p = 0.21).

In the initial CABG group, repeat revascularization was not a predictor of the composite safety endpoint (HR: 0.92; 95% CI: 0.54 to 1.75; p = 0.92). However, although repeat PCI after initial CABG was not a predictor (HR: 0.69; 95% CI: 0.34 to 1.37; p = 0.28), repeat CABG was associated with the composite safety endpoint (HR: 3.32; 95% CI: 1.21 to 9.11; p = 0.020). Neither TLR nor de novo lesion revascularization were found to be independent predictors of the composite safety endpoint (HR: 1.06; 95% CI: 0.50 to 2.22; p = 0.89; and HR: 0.67; 95% CI: 0.27 to 1.67; p = 0.39, respectively).

Considering not only events occurring after repeat revascularization but also before repeat revascularization, the results were similar (Supplemental Appendix).

Table 2. Baseline and Procedural Characteristics.

	PCI Group (n = 903)			CABG Group (n = 897)		
	Repeat Revascularization Group (n = 220)	No-Repeat Revascularization Group (n = 683)	p Value	Repeat Revascularization Group (n = 110)	No-Repeat Revascularization Group (n = 787)	p Value
Clinical characteristics						
Age, yrs	64.8 ± 9.2	65.4 ± 9.8	0.45	63.4 ± 9.0	65.2 ± 9.9	0.07
Female	24.5 (54)	23.3 (159)	0.70	18.2 (20)	21. (169)	0.43
Non-White	5.0 (11)	2.3 (16)	0.044	8.2 (9)	3.9 (31)	0.08
Enrolled in the United States	14.1 (31)	13.5 (92)	0.82	22.7 (25)	12.3 (97)	0.003
Risk factors						
Family history of CAD	24.5 (52)	26.9 (174)	0.51	29.7 (30)	27.2 (205)	0.60
Hypertension	75.2 (164)	73.6 (499)	0.63	76.9 (83)	77.0 (603)	0.97
Hyperlipidemia	81.6 (177)	77.8 (528)	0.23	80.0 (88)	76.8 (598)	0.45
Medically treated DM	34.1 (75)	22.8 (156)	0.001	25.5 (28)	24.5 (193)	0.83
Insulin	15.9 (35)	7.9 (54)	0.001	13.6 (15)	9.9 (78)	0.23
Noninsulin	20.9 (46)	17.6 (120)	0.27	16.4 (18)	18.4 (145)	0.60
Current smoker	15.9 (35)	19.3 (132)	0.26	20.9 (23)	22.2 (173)	0.76
Previous MI	33.2 (72)	31.5 (213)	0.65	24.5 (27)	35.1 (273)	0.028
Previous CHF	4.6 (10)	3.8 (26)	0.63	7.3 (8)	5.1 (770)	0.34
Unstable angina	31.4 (69)	28.3 (193)	0.38	33.6 (37)	27.2 (214)	0.16
Peripheral artery disease	9.5 (21)	8.9 (61)	0.78	12.7 (14)	10.3 (81)	0.44
Carotid artery disease	10.0 (22)	7.5 (51)	0.23	4.5 (5)	8.9 (70)	0.12
Previous TIA/CVA	6.8 (15)	7.9 (54)	0.59	8.2 (9)	9.3 (72)	0.72
COPD	9.1 (20)	7.5 (51)	0.44	8.2 (9)	9.4 (74)	0.68
Renal impairment	0.5 (1)	1.3 (9)	0.47	0.9 (1)	1.9 (15)	0.71
BMI, kg/m^2	28.4 ± 4.8	28.0 ± 4.8	0.39	27.9 ± 4.8	27.9 ± 4.5	0.92
Logistic EuroSCORE	3.5 ± 3.3	3.9 ± 4.9	0.34	3.0 ± 2.8	4.0 ± 4.6	0.001
LVEF <50%	17.8 (38)	20.1 (134)	0.48	14.5 (16)	20.4 (159)	0.15
Coronary complexity						
3VD	59.1 (131)	60.9 (416)	0.63	55.5 (61)	62.0 (487)	0.19
Left main	40.9 (90)	39.1 (267)	0.63	44.5 (49)	38.0 (229)	0.19
LCA	89.5 (197)	89.3 (610)	0.92	84.5 (93)	89.6 (704)	0.12
LCxA	89.5 (197)	84.2 (575)	0.05	84.5 (93)	83.6 (657)	0.80
RCA	86.8 (191)	80.5 (550)	0.034	78.2 (86)	81.6 (641)	0.40
No. of lesions	4.5 ± 1.7	4.3 ± 1.8	0.06	4.3 ± 1.9	4.4 ± 1.8	0.65
SYNTAX Score	26.6 ± 10.3	24.7 ± 10.6	0.023	24.5 ± 9.7	24.7 ± 10.0	0.84

Table 2. Continued.

Procedural characteristics						
Total stents	5.1 ± 2.4	4.5 ± 2.2	0.001			
Total stent length	91.7 ± 51	84.7 ± 47	0.07			
Total overlapping stents	0.7 ± 0.7	0.6 ± 0.6	0.015			
Staged procedure	17.7 (39)	12.6 (86)	0.06			
On pump				75.5 (83)	80.2 (631)	0.25
Off pump				20.6 (22)	14.2 (106)	0.09
Arterial conduits				1.5 ± 0.7	1.4 ± 0.6	0.048
Venous conduits				1.2 ± 1.0	1.4 ± 0.9	0.07
Distal anastomoses				3.1 ± 0.9	3.2 ± 0.9	0.28
Grafts per patient				2.7 ± 0.7	2.8 ± 0.7	0.76
LIMA				98.1 (105)	96.7 (722)	0.56
Radial artery				20.6 (22)	13.1 (98)	0.038
BIMA				32.7 (35)	26.9 (201)	0.21
Second arterial graft				43.0 (46)	34.3 (256)	0.08
Complete arterial				28.0 (30)	17.4 (130)	0.008
Incomplete revascularization	53.6 (118)	39.9 (270)	<0.001	36.1 (274)	43.3 (388)	0.24
Revascularization priority*†						
Elective	92.3 (203)	94.7 (640)	0.57	90.9 (100)	92.5 (703)	1.00
Urgent	5.5 (12)	3.7 (25)	0.78	1.8 (2)	4.1 (31)	1.00
Emergent	2.3 (5)	1.6 (11)	1.00	7.3 (8)	3.4 (26)	0.18
Medication at discharge						
ASA	94.1 (207)	97.0 (656)	0.0044	97.3 (107)	87.2 (663)	0.002
Thienopyridine	93.6 (206)	87.8 (661)	0.003	25.5 (28)	18.7 (142)	0.09
Statins	84.5 (186)	87.4 (591)	0.27	70.9 (78)	75.0 (570)	0.36

Values are mean ± SD or % (n). *Elective: scheduled in advance as it does not involve a medical emergency; urgent: can wait until the patient is stable; emergent: no choice but immediate intervention.
†Bonferroni correction method for multiple comparisons.
3VD, 3-vessel disease; ASA, acetylsalicylic acid; BIMA, bilateral mammary artery; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular event(s); DM, diabetes mellitus; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LCA, left coronary artery; LCxA, left circumflex artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; RCA, right coronary artery; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery; TIA, transient ischemic attack; other abbreviations as in Table 1.

Table3. Independent Predictors of Repeat Revascularization.

	HR	95% CI	p Value
PCI group (n = 903)			
Medically treated DM	1.59	1.20–2.12	0.001
Number of overlapping stents	1.34	1.09–1.64	0.005
Incomplete revascularization	1.54	1.17–2.02	0.002
No ASA at discharge	2.18	1.23–3.85	0.008
No thienopyridine at discharge	6.03	3.36–10.8	<0.001
CABG group (n = 897)			
United States vs. Europe	1.75	1.09–2.81	0.020
Left coronary artery lesion	0.55	0.32–0.94	0.028
Off pump	1.51	0.94–2.44	0.091
No ASA at discharge	0.25	0.08–0.80	0.019
Statins at discharge	0.64	0.42–0.97	0.036

ASA, acetylsalicylic acid; CI confidence interval; HR, hazard ratio; other abbreviations as in Tables 1 and 2.

Table 4. Periprocedural Mortality and Morbidity.

	Type of Repeat Revascularization						Urgency of Repeat Revascularizations					
	All Repeat Revascularizations			PCI Repeat Revascularizations			Elective*			Urgent		
	PCI Group (n = 220)	CABG Group (n = 110)	p Value	PCI Group (n = 183)	CABG Group (n = 102)	p Value	PCI Group (n = 97)	CABG Group (n = 65)	p Value	PCI Group (n = 123)	CABG Group (n = 45)	p Value
Events <30 days of repeat revascularization												
Composite endpoint‡	22.7%	11.8%	0.017	24.0%	11.8%	0.012	6.2%	4.6%	0.74	35.8%	22.2%	0.096
Subsequent repeat revascularization	10.0%	7.3%	0.42	12.0%	7.8%	0.27	4.1%	4.6%	1.00	13.8%	8.9%	0.39
Myocardial infarction	15.0%	3.6%	0.002	16.4%	3.9%	0.002	1.0%	1.5%	1.00	26.0%	6.7%	0.006
Death	7.3%	1.8%	0.040	6.6%	1.0%	0.031	1.0%	0%	1.00	12.2%	4.4%	0.25
Events <30 days of repeat revascularization, excluding myocardial infarction on the same day												
Composite endpoint‡	13.6%	9.1%	0.23	14.2%	8.8%	0.18	6.2%	4.6%	0.74	19.5%	15.6%	0.59
Subsequent repeat revascularization	8.6%	7.3%	0.67	10.4%	7.8%	0.48	5.2%	4.6%	1.00	11.4%	11.1%	0.96
Myocardial infarction	0.9%	0%	0.55	1.1%	0%	0.54	0%	0%	1.00	1.6%	0%	1.00
Death	5.5%	1.8%	0.15	4.4%	1.0%	0.16	1.0%	0%	1.00	8.9%	4.4%	0.52

*Elective repeat revascularization consists of procedures performed for stable angina pectoris or silent myocardial ischemia. †Urgent repeat revascularization consists of procedures performed for unstable angina pectoris or acute myocardial infarction. ‡Each patient may have had more than 1 event in each category.

Abbreviations as in Table 1.

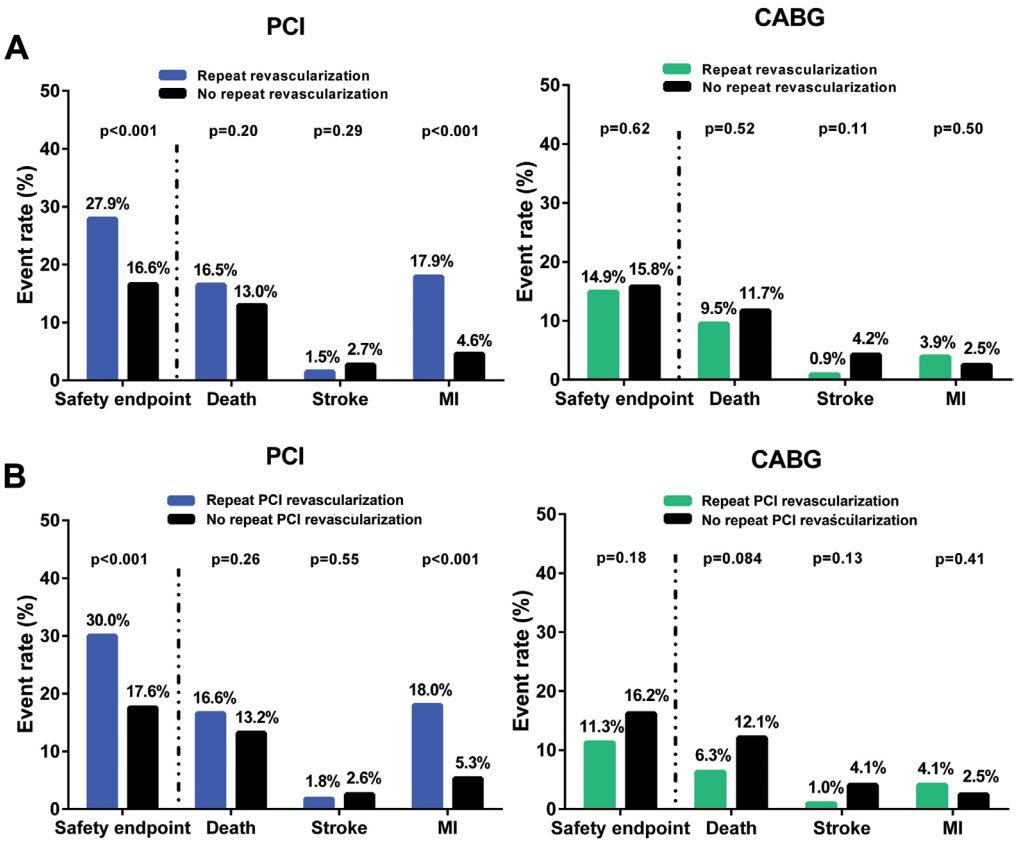
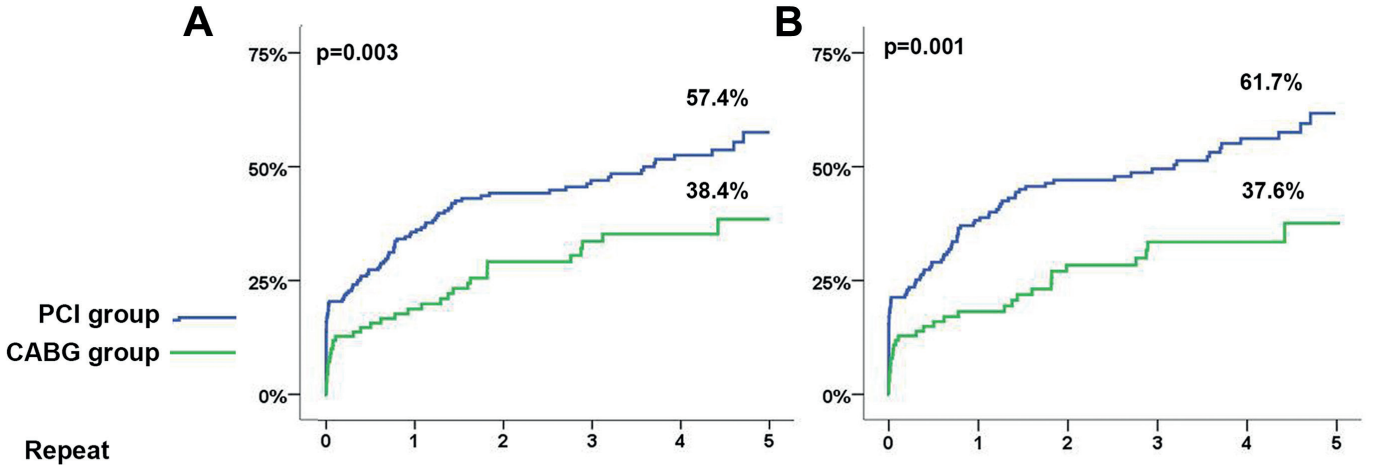


Figure 4. Clinical Outcomes After PCI and CABG With or Without Repeat Revascularization During Follow-Up. Rates of the composite safety endpoint of all-cause death, stroke, and myocardial infarction are compared between patients who required **(A)** any repeat revascularization or **(B)** only repeat PCI revascularization and those who did not require repeat revascularization. Safety endpoint was the composite endpoint of all-cause death, stroke, and myocardial infarction (MI). Abbreviations as in Figure 1.

DISCUSSION

The present study is the first in-depth analysis of repeat revascularization from any randomized trial comparing CABG with PCI, whose findings are essential in understanding the underlying mechanisms of clinical differences between CABG and PCI, and provide insights into potential improvements in both surgical and interventional treatment. The main findings are that: 1) repeat revascularization rates were significantly higher after PCI compared with CABG at early, intermediate, and long-term intervals, and more often consisted of multiple repeat revascularizations during follow-up; 2) in agreement with available



Repeat revascularization type	All repeat revascularization			PCI repeat revascularization		
Index procedure	PCI group (n=220)	CABG group (n=110)	p-value	PCI group (n=183)	CABG group (n=102)	p-value
Composite endpoint	57.4%	38.4%	0.003	61.7%	37.6%	0.001
2nd+ Revascularization	43.4%	25.3%	0.012	50.9%	27.1%	0.002
Myocardial infarction	19.2%	4.8%	0.001	18.6%	5.3%	0.001
Death	20.2%	13.9%	0.095	20.6%	11.5%	0.021

Figure 5. Kaplan-Meier Estimates of the Composite Safety Endpoint After Repeat Revascularization. Kaplan-Meier estimates after the **(A)** first revascularization and **(B)** first PCI repeat revascularization during follow-up after initial PCI (blue line) or CABG (green line). Comparisons between index procedure in patients with **(A)** any repeat revascularization reveal a hazard ratio of 0.46 (95% confidence interval: 0.26 to 0.82; p = 0.008). The p values in figures are by log-rank test. Abbreviations as in Figure 1.

guidelines, repeat revascularizations were most frequently performed by means of PCI after both initial PCI and initial CABG (13,14); 3) the consequences of repeat revascularization were apparent in the short term and comparable between PCI and CABG, whereas long-term rates of all-cause death, stroke, and MI were significantly higher after repeat revascularization after initial PCI but not initial CABG; and 4) long-term outcomes were comparable among patients not requiring repeat revascularization after either initial PCI or initial CABG.

Data from large PCI trials have demonstrated incremental technical advances over time, with the latest generation of drug-eluting stents (DES) achieving the lowest rates of restenosis, stent thrombosis, and recurrent MI that may all account for repeat revascularization (15). In ARTS-I (Arterial Revascularization Therapies Study), use of baremetal stents in the PCI group led to a repeat revascularization rate of 30.3%, whereas use of DES in the ARTS-II and SYNTAX trial was associated with lower repeat revascularization rates (20.3% and 25.9%, respectively) (7,16). The current study was performed with first-generation DES and showed that repeat revascularization rates were still about twice as high after PCI than after CABG during 5-year follow-up. It has been suggested that outcomes would have been different had a second-generation DES been used (17). However, the recent results from the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial showed that even with the use of second-generation everolimus-eluting stents for multivessel disease, CABG results were significantly better than PCI at 5-year follow-up due to a reduction in repeat revascularization as well as spontaneous MI (18).

In the current study, repeat revascularization after initial PCI consisted mainly of TVR and less for de novo lesions. It appears that both progression of disease and stent restenosis or thrombosis are more prominent after initial PCI than after initial CABG treatment. By placing anastomoses distal to potential future lesions, CABG may have a protective effect from repeat revascularization, although it does not prevent future lesions (19). The introduction of nextgeneration DES is encouraging with reduced rates of stent thrombosis and TVR that may potentially mitigate the differences between PCI and CABG (20,21), but their use will not eliminate later revascularization for de novo lesions. Assessment of long-term results and trials comparing these stents with CABG are required to assess whether reductions in TLR are sufficient to provide noninferior outcomes to CABG (22).

Table 5. Predictors of the Composite Safety Endpoint of All-Cause Death, Stroke, and MI.

	HR	Model 1* 95% CI	p Value	HR	Model 2† 95% CI	p Value	HR	Model 3‡ 95% CI	p Value
PCI group (n = 903)									
Age (yrs)	1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
Previous MI	1.62	1.19–2.20	0.002	1.65	1.22–2.25	0.001	1.64	1.21–2.23	0.002
PAD	2.03	1.35–3.07	0.001	2.05	1.36–3.09	0.001	2.03	1.34–3.08	0.001
Staged procedure	1.83	1.26–2.59	0.002	1.80	1.24–2.61	0.002	1.82	1.25–2.64	0.002
No ASA	2.47	1.43–4.24	0.001	2.45	1.42–4.21	0.001	2.55	1.49–4.37	0.001
No thienopyridine	3.79	2.12–6.77	<0.001	3.63	2.01–6.57	<0.001	3.92	2.20–6.99	<0.001
Statins	0.61	0.41–0.90	0.013	0.60	0.41–0.89	0.012	0.61	0.41–0.91	0.015
All repeat revascularization*	1.65	1.20–2.27	0.002		Not included			Not included	
PCI repeat revascularization†		Not included		1.67	1.20–2.32	0.002		Not included	
CABG repeat revascularization†		Not included		1.72	1.02–2.88	0.041		Not included	
Target lesion revascularization		Not included			Not included		1.69	1.20–2.38	0.003
De novo lesion revascularization		Not included			Not included		1.49	0.80–2.79	0.21
CABG group (n = 897)									
Age (yrs)	1.07	1.04–1.09	<0.001	1.07	1.04–1.09	<0.001	1.07	1.04–1.09	<0.001
COPD	1.88	1.27–3.29	0.013	1.87	1.17–3.05	0.014	1.82	1.11–2.99	0.017
PAD	2.54	1.34–3.08	<0.001	2.58	1.27–3.06	<0.001	2.51	1.65–3.81	<0.001
Renal impairment	2.63	1.17–6.16	0.023	2.47	1.38–3.16	0.034	2.56	1.12–5.87	0.028
SYNTAX score	1.02	1.00–1.04	0.078	1.02	1.00–1.04	0.10	1.02	1.00–1.03	0.07
No ASA	2.31	1.41–3.30	<0.001	2.29	1.34–3.09	<0.001	2.32	1.52–3.55	<0.001
Statins	0.48	0.36–0.72	<0.001	0.48	0.34–0.69	<0.001	0.47	0.33–0.68	<0.001
All repeat revascularization*	0.92	0.54–1.75	0.92		Not included			Not included	
PCI repeat revascularization†		Not included		0.69	0.34–1.37	0.28		Not included	
CABG repeat revascularization†		Not included		3.32	1.21–9.11	0.020		Not included	
Target lesion revascularization		Not included			Not included		1.06	0.50–2.22	0.89
De novo lesion revascularization		Not included			Not included		0.67	0.27–1.67	0.39

*Repeat revascularization (PCI or CABG) is included as separate variable in Model 1. †PCI repeat revascularization and CABG repeat revascularization are included as separate variables in Model 2. ‡Target lesion revascularization and de novo lesion revascularization are included as separate variables in Model 3. Bold values indicate variables of repeat revascularization.
PAD, peripheral artery disease; other abbreviations as in Tables 1, 2, and 3.

According to our data, reductions in repeat revascularization are translated into improved outcomes in clinical endpoints, particularly MI. In the short-term, repeat revascularization was associated with increased periprocedural mortality and morbidity, which is more prominent after initial PCI than initial CABG treatment, likely to be the result of more acute presentation. Therefore, as repeat revascularization can also be a life-saving procedure in the setting of an acute MI, it is important to mention that by excluding events occurring at the same day of

repeat revascularization (the majority consisting of MI), the difference between initial PCI and CABG was no longer statistically significant, referring only to the intrinsic risk of the procedure. In the long-term, repeat revascularization was associated with increased rates of the composite safety endpoint, even after adjustment for baseline and procedural characteristics. Comparing PCI and CABG in the context of comparable rates of all-cause death and competing risks with repeat revascularization that are overestimated by Kaplan-Meier methods (23), patients undergoing initial PCI were more likely to return for repeat revascularization than those who underwent initial CABG, possibly particularly the result of preceding MI. As no difference was noted between initial PCI and initial CABG among patients who did not undergo repeat revascularization, the importance of identifying patients at risk for revascularization must be underlined.

In our analyses we were unable to identify a set of baseline clinical variables that could identify patients in whom initial PCI offers similar results as initial CABG in terms of repeat revascularization and long-term clinical outcomes as a result of these interventions. However, we were able to identify patients at highest risk for repeat revascularization for whom specific treatment for appropriate riskreduction would apply. The complexity of disease was not a predictor, unlike findings of other studies (24,25). Nevertheless, incomplete revascularization and the number of overlapping stents that are highly correlated to the SYNTAX score (26), were independent predictors of repeat revascularization (4). These findings underline the need for routine use of fractional flow reserve that has been shown to reduce the number of stents used during PCI with subsequent reductions in adverse events (27). Furthermore, in alignment with randomized trials evaluating post-PCI antiplatelet therapy and current guidelines, we found that nonuse of acetylsalicylic acid or thienopyridine predicted repeat revascularization (28,29), and medical therapy was also a predictor of worse long-term outcomes (30). Paradoxically, patients requiring repeat revascularization after initial CABG had less presence of comorbidities and qualified as lower risk at the time of the initial procedure (3). Off-pump CABG and enrollment in the United States versus Europe were independent predictors of repeat revascularization, most probably due to a more proactive approach for repeat revascularization in case of symptoms recurrence after initial CABG (31). Whether incomplete revascularization is an important factor when performing CABG, remains a matter of debate (32,33). Some data suggest that incomplete revascularization has a particular impact on the repeat revascularization rate (34), but incomplete revascularization after CABG failed to be an independent predictor in the current analysis. Similar to

the findings in the PCI group, secondary prevention measures remain critical in reducing adverse events, including repeat revascularization (35). Not included in multivariable models, but an area in which CABG outcomes can be improved, is early post-operative complications (36). Many repeat CABG revascularizations were the result of early complications (hemorrhage or acute graft failure) after initial CABG, for which intraoperative graft flow measurements may prove beneficial, although no consensus has been reached over their use (35–37).

STUDY LIMITATIONS. The present study is a post hoc analysis of the SYNTAX trial and the results should therefore be interpreted within the limits of both statistical power and clinical relevance. The SYNTAX trial did not primarily intend to investigate the practice of repeat revascularization, although repeat revascularization was registered as a component of the primary endpoint under supervision of the independent Clinical Events Committee and was a standalone secondary endpoint. Angiography was not routinely performed and there are no available data on the use of fractional flow reserve or functional testing in the assessment of lesions.

CONCLUSIONS

Repeat revascularization is not a benign event as patients requiring repeat revascularization are at increased risk of both periprocedural and long-term events. Predictors of patients at risk for repeat revascularization highlight the need for adequate medical treatment as secondary prevention. Although procedural risk of repeat revascularization is similar after initial PCI and CABG procedure, long-term results show higher rates of clinically meaningful endpoints after repeat revascularization in the PCI group, which drove the differences favoring CABG over PCI in the more complex patients in the SYNTAX trial overall. However, comparison of long-term results of patients who did not undergo repeat revascularization revealed similar outcomes between PCI and CABG, suggesting that both careful patient selection and improvements in both PCI and CABG technology, techniques, and adjunctive therapies will have a favorable impact in the future.

CLINICAL PERSPECTIVES

WHAT IS NEW? Repeat revascularization is a biased clinical outcome from randomized trials comparing PCI with CABG with limited in-depth long-term follow-up data available. This study therefore aimed to analyze the incidence, characteristics, and predictors of repeat revascularization as well as its long-term impact on hard clinical events during 5-year follow-up of the SYNTAX trial.

WHAT IS KNOWN? Repeat revascularization occurred more often after PCI than after CABG, and more often consisted of multiple repeat revascularizations. Significantly more repeat PCI procedures were performed on de novo lesions in patients after initial PCI than initial CABG. Repeat revascularization was an independent predictor of the composite safety endpoint of death, MI, and stroke after both treatment types for complex coronary artery disease.

WHAT IS NEXT? Careful selection of patients, use of novel interventional devices and functional assessment, together with aggressive medical therapy, should be the main approach in reducing the rate of repeat revascularization and the negative impact it has on clinical outcomes.

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SUPPLEMENTAL MATERIAL

APPENDIX 1.

Variables included and excluded in the models to identify independent predictors of repeat revascularization.

PCI model:

Variables considered in univariate analysis: age, gender, hypertension, hyperlipidemia, unstable angina, history of myocardial infarction, history of heart failure, history of TIA/CVA, peripheral vessel disease, carotid artery disease, renal impairment, current smoker, medically treated diabetes mellitus, insulin-dependent diabetes mellitus, impaired left ventricular ejection fraction, SYNTAX Score, staged procedure, incomplete revascularization, total stents, total stent length, number of overlapping stents, RCA lesions, LCxA lesion, no ASA at discharge, no thienopyridine at discharge, statins at discharge.

Included in multivariate model: age, SYNTAX Score, medically treated diabetes mellitus, incomplete revascularization, staged procedure, number of overlapping stents, no ASA at discharge, no thienopyridine at discharge, statins at discharge.

Excluded from multivariate model because of high correlates: number of lesions, RCA lesion, LCxA lesion, number of stents, insulin-dependent diabetes mellitus.

CABG model:

Variables considered in univariate analysis: age, gender, enrolment in the United States vs. Europe, hyperlipidemia, hypertension, diabetes mellitus, type 1 diabetes, type 2 diabetes, medically treated diabetes, insulin treated diabetes, non-insulin treated diabetes, diet treatment diabetes, previous myocardial infarction, previous congestive heart failure, unstable angina, peripheral vascular disease , previous TIA/stroke, renal impairment, SYNTAX Score, number of lesions, LM lesion, LCA lesion, RCA lesion, LCxA lesion, off-pump CABG, crystalloid cardioplegia, blood cardioplegia, total arterial conduits, total venous conduits, left intermal mammary artery use, radial artery use, bilateral internal mammary artery use, more than one arterial conduit, complete arterial, distal anastomoses, grafts, incomplete revascularization, no ASA at discharge, no thienopyridine at discharge, no antiplatelet at discharge, statins at discharge.

Included in multivariate model: LCA lesion, SYNTAX Score, more than one arterial conduit, incomplete revascularization, off-pump CABG, enrolment in the US vs. Europe, statins at discharge, no ASA at discharge, previous MI, previous CHF.

Excluded from multivariate model because of high correlates: radial artery use, complete arterial.

APPENDIX 2.

Variables included in the models to adjust for repeat revascularization as independent predictors of death, MI and stroke during follow-up.

PCI model:

Variables considered in univariate analysis: age, gender, hyperlipidemia, hypertension, diabetes mellitus, medically treated diabetes, insulin-dependent diabetes, previous myocardial infarction, previous congestive heart failure, unstable angina, chronic obstructive pulmonary disease, peripheral vascular disease, carotid disease, renal impairment, SYNTAX Score, number of lesions, staged procedure, number of stents, number of overlapping stents, incomplete revascularization, no ASA at discharge, no thienopyridine at discharge, statins at discharge.

Included in the multivariate model: age, previous myocardial infarction, peripheral vessel disease, staged procedure, incomplete revascularization, no ASA at discharge, no thienopyridine at discharge, and statins at discharge.

Excluded from multivariate model because of high correlates: medically treated DM, insulin-dependent DM.

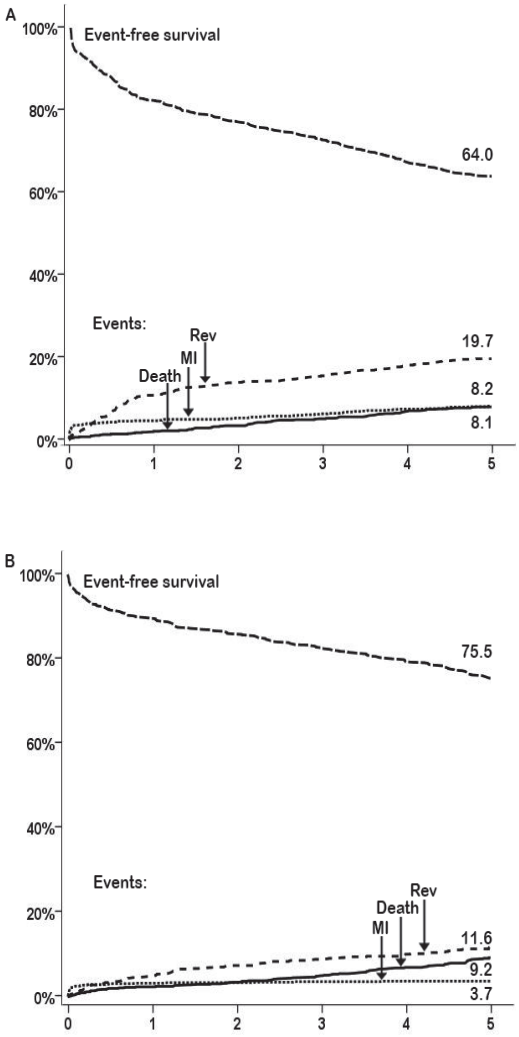
CABG model:

Variables considered in univariate analysis: age, gender, hyperlipidemia, hypertension, diabetes mellitus, medically treated diabetes, insulin-dependent diabetes, previous myocardial infarction, previous congestive heart failure, unstable angina, chronic obstructive pulmonary disease, peripheral vascular disease, carotid disease, renal impairment, SYNTAX score, off-pump CABG, crystalloid cardioplegia, blood cardioplegia, more 1 arterial conduit, distal anastomoses, grafts incomplete revascularization, no ASA at discharge, no thienopyridine at discharge, statins at discharge.

Included in the multivariate model: age, chronic obstructive pulmonary disease, peripheral vessel disease, renal impairment, SYNTAX Score, blood cardioplegia, no ASA at discharge, statins at discharge.

Excluded from multivariate model because of high correlates: medically treated DM, insulin-dependent DM.

APPENDIX 3.



Estimates of the cumulative incidence of adverse events after initial PCI (A) and CABG (B) in the presence of competing risks. The percentage of patients in each category sums up to 100% at all time points during follow-up. Rev, repeat revascularization; MI, myocardial infarction.

APPENDIX 4.

Univariate analysis to identify independent predictors of repeat revascularization in PCI and CABG group.

PCI group (n=903)				CABG group (n=897)			
Baseline characteristics	**HR**	**95% CI**	**p-value**	**Baseline characteristics**	**HR**	**95% CI**	**p-value**
Age	1.00	0.99-1.01	0.82	Age	0.99	0.97-1.01	0.15
Gender, female	1.08	0.80-1.47	0.62	Gender, female	0.86	0.53-1.39	0.54
Hyperlipidemia	1.20	0.85-1.68	0.31	Enrolment in US	2.06	1.32-3.22	0.001
Hypertension	1.11	0.82-1.51	0.51	Hyperlipidemia	1.17	0.73-1.86	0.51
Medically treated DM	1.70	1.29-2.24	<0.001	Hypertension	1.06	0.68-1.66	0.79
Insulin-dependent DM	2.04	1.42-2.92	<0.001	Medically treated DM	1.12	0.73-1.72	0.60
Previous MI	1.09	0.82-1.45	0.54	Insulin treated DM	1.48	0.86-2.56	0.16
Previous CHF	1.16	0.61-2.19	0.65	Previous MI	0.64	0.42-0.99	0.044
Unstable angina	1.18	0.89-1.57	0.25	Previous CHF	1.67	0.82-3.44	0.16
Current smoker	0.85	0.59-1.22	0.38	Unstable angina	1.39	0.94-2.06	0.10
PAD	1.21	0.77-1.90	0.40	PAD	1.47	0.84-2.58	0.18
Renal impairment	0.47	0.07-3.38	0.46	Previous TIA/CVA	0.91	0.46-1.81	0.79
Previous TIA/CVA	0.92	0.55-1.56	0.76	Renal impairment	0.67	0.09-4.79	0.69
Anatomic characteristics				**Anatomic characteristics**			
SYNTAX score	1.01	1.00-1.02	0.035	SYNTAX score	1.00	0.98-1.02	0.88
Number of lesions	1.10	1.01-1.18	0.015	LM lesion	1.28	0.88-1.87	0.20
LM lesion	1.03	0.79-1.35	0.81	LCA lesion	0.65	0.39-1.10	0.11
RCA lesion	1.55	1.05-2.30	0.027	RCA lesion	0.85	0.54-1.33	0.47
LCxA lesion	1.62	1.05-2.49	0.029	LCxA lesion	1.09	0.65-1.83	0.75
Procedure characteristics				**Procedure characteristics**			
Number of stents	1.10	1.04-1.16	0.001	Off-pump	1.63	1.02-2.60	0.042
Total stents length	1.00	1.00-1.01	0.07	Crystalloid cardioplegia	1.05	0.71-1.57	0.80
Number of overlapping stents	1.31	1.07-1.60	0.008	Blood cardioplegia	0.77	0.53-1.13	0.18
Staged procedure	1.45	1.02-2.05	0.036	Total arterial conduits	1.32	1.01-1.72	0.045
Incomplete revascularization	0.60	0.46-0.78	<0.001	Total venous conduits	0.83	0.67-1.03	0.09
Discharge medication				LIMA use	1.73	0.55-5.46	0.35
No ASA	2.45	1.40-4.29	0.002	RA use	1.58	0.99-2.53	0.055
No thienopyridine	4.01	2.33-6.90	<0.001	BIMA use	1.25	0.83-1.87	0.29
No antiplatelet	41.2	16.5-102.6	<0.001	2nd arterial graft	1.35	0.92-1.98	0.12
Statins	0.73	0.51-1.06	0.10	Complete arterial	1.70	1.11-2.59	0.014
				Distal anastomoses	0.88	0.71-1.10	0.26

Appendix 4 Continued.

	Grafts	0.96	0.74-1.26	0.78
	Incomplete revascularization	1.28	0.87-1.86	0.21
	Discharge medication			
	No ASA	0.24	0.08-0.76	0.015
	No thienopyridine	0.69	0.45-1.06	0.09
	No antiplatelet	0.46	0.15-1.44	0.18
	Statins	0.75	0.50-1.14	0.18

ASA, acetylsalicylic acid; BIMA, bilateral mammary artery; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; LCA, Left coronary artery; LCxA, Left circumflex artery; LM, left main; LIMA, Left internal mammary artery; MI, myocardial infarction; PAD, peripheral artery disease; RA, radial artery; RCA, Right coronary artery; TIA, transient ischemic attack.

APPENDIX 5.

Univariate and multivariate analyses to identify independent predictors of adverse events in PCI and CABG group, respectively (only events occurring after repeat revascularization).

PCI (n=903)	Univariate analysis			Model 1*			Model 2**			Model 3***		
Baseline characteristics (Block 1)	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.04	1.02-1.05	<0.001	1.03	1.02-1.05	<0.001	1.03	1.02-1.05	<0.001	1.03	1.02-1.05	<0.001
Gender, female	1.34	0.96-1.86	0.09									
Hyperlipidemia	0.81	0.57-1.15	0.23									
Hypertension	1.35	0.93-1.95	0.11									
Diabetes mellitus	1.31	0.96-1.80	0.09									
Medically treated DM	1.32	0.95-1.83	0.09									
Insulin treatment	1.89	1.25-2.85	0.002									
Previous MI	1.61	1.19-2.18	0.002	1.62	1.19-2.20	0.002	1.65	1.22-2.25	0.001	1.64	1.21-2.23	0.002
Previous CHF	1.56	0.82-2.96	0.17									
Unstable angina	1.45	1.07-1.99	0.018									
COPD	1.55	0.96-2.50	0.07									
PAD	2.26	1.51-3.39	<0.001	2.03	1.35-3.07	0.001	2.05	1.36-3.09	0.001	2.03	1.34-3.08	0.001
CAD	1.74	1.10-2.75	0.018									
Renal impairment	2.66	0.99-7.16	0.054									
Anatomic characteristics												
SYNTAX Score	1.01	1.00-1.02	0.17									
Number of lesions	1.09	1.00-1.19	0.04									
Procedure characteristics												
Staged procedure	1.79	1.25-2.58	0.002	1.83	1.26-2.59	0.002	1.80	1.24-2.61	0.002	1.82	1.25-2.64	0.002
Number of stents	1.06	1.00-1.13	0.07									
Number of overlapping stents	1.11	0.88-1.40	0.39									
Incomplete revascularization	1.45	1.07-1.96	0.015									
Discharge medication												
No ASA	4.22	2.55-6.96	<0.001	2.47	1.43-4.24	0.001	2.45	1.42-4.21	0.001	2.55	1.49-4.37	0.001
No Thienopyridine	4.27	2.47-7.37	<0.001	3.79	2.12-6.77	<0.001	3.63	2.01-6.57	<0.001	3.92	2.20-6.99	<0.001
Statins	0.56	0.39-0.82	<0.001	0.61	0.41-0.90	0.013	0.60	0.41-0.89	0.012	0.61	0.41-0.91	0.015

Appendix 5. Continued.

Repeat revascularization (Block 2)												
*Secondary PCI or CABG	1.80	1.32-2.46	<0.001	**1.65**	**1.20-2.27**	**0.002**		Not included			Not included	
**Secondary PCI	1.74	1.26-2.42	0.001		Not included		**1.67**	**1.20-2.32**	**0.002**		Not included	
**Secondary CABG	1.89	1.15-3.12	0.012		Not included		**1.72**	**1.02-2.88**	**0.041**		Not included	
***Target lesion (TLR)	1.85	1.32-2.59	<0.001		Not included			Not included		**1.69**	**1.20-2.38**	**0.003**
***De novo lesion	1.52	0.83-2.80	0.18		Not included			Not included		**1.49**	0.80-2.79	0.21
CABG (n=897)	Univariate analysis			Model 1*			Model 2**			Model 3***		
Baseline characteristics (Block 1)	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.07	1.05-1.10	<0.001	1.07	1.04-1.09	<0.001	1.07	1.04-1.09	<0.001	1.07	1.04-1.09	<0.001
Gender, female	1.07	0.70-1.62	0.76									
Hyperlipidemia	0.71	0.49-1.05	0.08									
Hypertension	1.72	1.07-2.77	0.026									
Diabetes mellitus	1.30	0.90-1.87	0.16									
Medically treated DM	1.22	0.83-1.78	0.32									
Insulin treatment	1.24	0.73-2.08	0.43									
Previous MI	0.88	0.61-1.28	0.50									
Previous CHF	2.36	1.32-4.18	0.003									
Unstable angina	0.94	0.641.38	0.75									
COPD	1.91	1.19-3.07	0.008	1.82	1.11-2.99	0.018	1.81	1.10-2.97	0.019	1.82	1.11-2.99	0.017
PAD	2.85	1.89-4.28	<0.001	2.45	1.61-3.72	<0.001	2.49	1.64-3.78	<0.001	2.51	1.65-3.81	<0.001
CAD	2.08	1.29-3.34	0.003									
Renal impairment	4.24	1.98-9.08	<0.001	2.59	1.13-5.96	0.025	2.44	1.06-5.62	0.036	2.56	1.12-5.87	0.028
Anatomic characteristics												
SYNTAX Score	1.02	1.01-1.04	0.005	1.02	1.00-1.03	0.068	1.02	1.00-1.03	0.086	1.02	1.00-1.03	0.07
Number of lesions	0.95	0.91-1.11	0.95									
Procedure characteristics												
Off pump	0.76	0.44-1.33	0.34									
Crystalloid cardioplegia	1.31	0.91-1.88	0.14									
Blood cardioplegia	0.74	0.53-1.04	0.09									
More 1 arterial conduit	1.15	0.36-3.60	0.82									
Distal anastomoses	0.83	0.68-1.03	0.09									
Grafts	0.80	0.62-1.03	0.09									
Incomplete revascularization	1.10	0.77-1.57	0.59									
Discharge medication												
No ASA	2.84	1.90-4.26	<0.001	2.37	1.55-3.63	<0.001	2.34	1.54-3.57	<0.001	2.32	1.52-3.55	<0.001

Appendix 5. Continued.

No Thienopyridine	1.05	0.68-1.64	0.82									
Statins	0.41	0.29-0.58	<0.001	0.48	0.33-0.69	<0.001	0.48	0.33-0.69	<0.001	0.47	0.33-0.68	<0.001
Repeat revascularization (Block 2)												
*Secondary PCI or CABG	0.87	0.51-1.49	0.62	**1.11**	**0.63-1.93**	**0.73**	Not included			Not included		
**Secondary PCI	0.66	0.36-1.22	0.19	Not included			**0.83**	**0.44-1.56**	**0.56**	Not included		
**Secondary CABG	2.87	1.06-7.76	0.038	Not included			**3.21**	**1.17-8.76**	**0.023**	Not included		
***Target lesion (TLR)	0.75	0.37-1.54	0.44	Not included			Not included			**1.06**	**0.50-2.22**	**0.89**
****De novo*** lesion	0.63	0.26-1.55	0.63	Not included			Not included			**0.67**	**0.27-1.67**	**0.39**

ASA, acetylsalicylic acid; BIMA, bilateral mammary artery; CHF, congestive heart failure; CAD, carotid artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease; RA, radial artery; RCA, Right coronary artery; TIA, transient ischemic attack; TLR, target lesion revascularization.

APPENDIX 6.

Univariate and multivariate analyses to identify independent predictors of adverse events in PCI and CABG group, respectively (all events occurring during 5-year follow-up).

PCI (n=867)	Univariate analysis			Model 1*			Model 2**			Model 3***		
Baseline characteristics (Block 1)	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.04	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001	1.04	1.02-1.06	<0.001
Gender, female	1.23	0.89-1.71	0.20									
Hyperlipidemia	0.84	0.60-1.18	0.30									
Hypertension	1.34	0.94-1.91	0.11									
Diabetes mellitus	1.22	0.90-1.67	0.20									
Medically treated DM	1.23	0.91-1.72	0.16									
Insulin treatment	1.79	1.20-2.67	0.005									
Non-insulin treatment	0.88	0.60-1.30	0.52									
Diet treatment	0.98	0.40-2.39	0.97									
Previous MI	1.73	1.30-2.32	<0.001	1.78	1.33-2.39	<0.001	1.84	1.37-2.47	<0.001	1.81	1.35-2.43	<0.001
Previous CHF	1.64	0.89-3.01	0.11									
Unstable angina	1.44	1.06-1.94	0.018									
COPD	1.71	1.10-2.67	0.018									
PAD	2.05	1.37-3.06	<0.001	1.84	1.22-2.76	0.003	1.86	1.24-2.80	0.003	1.84	1.22-2.78	0.004
CAD	1.58	1.00-2.49	0.048									
Renal impairment	2.43	0.90-6.53	0.08									
Anatomic characteristics												
SYNTAX Score	1.01	1.00-1.02	0.13									
Number of lesions	1.10	1.02-1.20	0.02									
Procedure characteristics												
Staged procedure	1.82	1.28-2.58	0.001	1.81	1.26-2.59	0.001	1.76	1.23-2.52	0.002	1.80	1.26-2.57	0.001
Number of stents	1.06	1.00-1.13	0.05									
Number of overlapping stents	1.17	0.94-1.46	0.16									
Incomplete revascularization	1.42	1.07-1.90	0.017									
Discharge medication												
No ASA	4.11	2.52-6.69	<0.001	2.19	1.29-3.72	0.004	2.19	1.29-3.73	0.004	2.35	1.40-3.96	0.001
No Thienopyridine	3.87	2.24-6.68	<0.001	3.23	1.81-5.77	<0.001	3.11	1.72-5.63	<0.001	3.50	1.97-6.22	<0.001
Statins	0.51	0.36-0.72	<0.001	0.52	0.36-0.76	0.001	0.52	0.36-0.75	0.001	0.53	0.37-0.77	0.001

Appendix 6. Continued.

Repeat revascularization (Block 2)												
*Secondary PCI or CABG	2.23	1.66-3.00	<0.001	**2.21**	**1.63-2.98**	**<0.001**		Not included			Not included	
**Secondary PCI	2.09	1.54-2.84	<0.001		Not included		**2.13**	**1.56-2.90**	**<0.001**		Not included	
**Secondary CABG	2.03	1.28-3.23	0.003		Not included		**2.01**	**1.24-3.26**	**0.005**		Not included	
***Target lesion(TLR)	2.17	1.58-2.98	<0.001		Not included			Not included		**2.09**	1.51-2.88	<0.001
****De novo*** lesion	1.69	0.96-2.97	0.07		Not included			Not included		**1.58**	**0.88-2.81**	**0.12**
CABG (n=897)	**Univariate analysis**			**Model 1***			**Model 2****			**Model 3*****		
Baseline characteristics (Block 1)	**HR**	**95% CI**	**p-value**	**HR**	**HR**	**HR**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.07	1.05-1.09	<0.001	1.06	1.04-1.09	<0.001	1.06	1.04-1.09	<0.001	1.06	1.04-1.08	<0.001
Gender, female	0.92	0.59-1.42	0.70									
Hyperlipidemia	0.73	0.50-1.08	0.11									
Hypertension	1.67	1.05-2.67	0.031									
Diabetes mellitus	1.34	0.93-1.91	0.11									
Medically treated DM	1.23	0.84-1.80	0.28									
Previous MI	0.88	0.61-1.28	0.51									
Previous CHF	2.17	1.20-3.93	0.010									
Unstable angina	1.08	0.75-1.57	0.68									
COPD	2.02	1.27-3.22	0.003	1.96	1.20-3.23	0.008	1.81	1.10-3.00	0.020	2.08	1.29-3.35	0.003
PAD	2.72	1.81-4.08	<0.001	1.93	1.25-3.00	0.003	1.97	1.27-3.06	0.002	2.13	1.41-3.23	<0.001
CAD	1.77	1.08-2.90	0.025									
Renal impairment	3.34	1.47-7.57	0.004	2.74	1.19-6.30	0.017	2.00	0.79-5.03	0.14	2.68	1.17-6.15	0.020
Anatomic characteristics												
SYNTAX Score	1.02	1.01-1.04	0.006	1.02	1.00-1.03	0.08	1.02	1.00-1.03	0.11	1.02	1.00-1.04	0.034
Number of lesions	0.99	0.91-1.09	0.90									
Procedure characteristics												
Off pump	0.93	0.56-1.54	0.76									
Crystalloid cardioplegia	1.30	0.92-1.84	0.14									
Blood cardioplegia	0.74	0.53-1.04	0.09	0.67	0.47-0.95	0.025	0.68	0.48-0.96	0.036	0.68	0.48-0.97	0.031
More 1 arterial conduit	0.69	0.48-1.00	0.05									
Distal anastomoses	0.87	0.72-1.06	0.18									
Grafts	0.80	0.63-1.02	0.07									

Appendix 6. Continued.

Incomplete revascularization	1.10	0.78-1.56	0.58									
Discharge medication												
No ASA	2.63	1.76-3.93	<0.001	1.97	1.26-3.07	0.003	1.87	1.21-2.90	0.005	2.09	1.37-3.20	0.001
No Thienopyridine	1.06	0.68-1.67	0.79									
Statins	0.42	0.30-0.60	<0.001	0.52	0.36-0.74	<0.001	0.50	0.35-0.71	<0.001	0.48	0.34-0.69	<0.001
Repeat revascularization (Block 2)												
*Secondary PCI or CABG	1.41	0.90-2.21	0.14	1.66	**1.03-2.69**	**0.039**		Not included			Not included	
**Secondary PCI	1.04	0.62-1.73	0.89		Not included		**1.09**	**0.63-1.90**	**0.75**		Not included	
**Secondary CABG	8.17	3.80-17.5	<0.001		Not included		**6.89**	**3.11-15.3**	**<0.001**		Not included	
***Target lesion(TLR)					Not included			Not included		**1.32**	**0.69-2.53**	**0.40**
****De novo*** lesion					Not included			Not included		**1.24**	**0.62-2.51**	**0.54**

ASA, acetylsalicylic acid; BIMA, bilateral mammary artery; CHF, congestive heart failure; CAD, carotid artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; MI, myocardial infarction; AD, peripheral artery disease; RA, radial artery; RCA, Right coronary artery; TIA, transient ischemic attack; TLR, target lesion revascularization.

Chapter 11

Hierarchical testing of composite endpoints: applying the win ratio to percutaneous coronary intervention versus coronary artery bypass grafting in the SYNTAX trial

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ABSTRACT

AIMS: The goal of the study was to compare long-term outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG), accounting for the clinical impact of individual components in the composite endpoints and prioritising these using the win ratio (Rw).

METHODS AND RESULTS: The win ratio was compared with conventional methods of analyses (hazard ratio (HR) and relative risk) in the SYNTAX trial (n=1,800). For the composite of death/stroke/myocardial infarction (MI), the win ratio favoured CABG and was 1.37 (95% CI: 1.10-1.77) for matched analysis, 1.28 (95% CI: 1.11-1.53) for unmatched analysis, while the conventional HR was 1.29 (95% CI: 1.11-1.53). The largest number of winners in favour of CABG over PCI were based on MI (n=39 vs. n=19, respectively). Death was significantly reduced with CABG in matched (Rw=1.39, 95% CI: 1.04-1.86) and unmatched win ratio analyses (Rw=1.27, 95% CI: 1.01-1.42) as compared with non-significant conventional analysis (HR 1.19, 95% CI: 0.92-1.56). In subgroups, matched win ratio analyses had a larger treatment effect in favour of CABG compared with conventional analyses, especially in patients with three-vessel disease and intermediate SYNTAX scores, while unmatched win ratios had a smaller point estimate, but with narrower confidence intervals than matched analyses findings.

CONCLUSIONS: This re-analysis of the SYNTAX trial using the win ratio shows that the most important benefit of CABG treatment is the reduction of hard clinical endpoints such as mortality and MI. Future trials using this approach can expect to maintain similar statistical power with smaller sample sizes, and thereby reduce the cost of a trial.

INTRODUCTION

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have been compared in many randomised clinical trials (1). These trials often used composite endpoints to obtain higher event rates and provide more statistical power, thus requiring smaller sample sizes, shorter follow-up, or both (2,3). However, composite endpoints are often criticised for having an intrinsic weakness, combining events with a very different impact on a patient's quality of life or life expectancy. The reporting of composite endpoints in clinical trials also has an inherent limitation in that it emphasises each patient's first event, which is often the outcome of lesser clinical importance.

The SYNTAX trial assessed the optimum revascularisation treatment for patients with *de novo* left main (LM) coronary disease and/or three-vessel disease (3VD), by randomly assigning patients to either CABG or PCI with a first-generation drug-eluting stent (DES). The primary endpoint was powered on non-inferiority of PCI versus CABG for the endpoint of major adverse cardiac and cerebrovascular events (MACCE), which is the composite of all-cause death, stroke, myocardial infarction (MI), and repeat revascularisation (4). The difference in MACCE between PCI and CABG was largely driven by higher rates of repeat revascularisation with PCI, which is thought to be a softer, less important endpoint, while rates of all-cause death were not significantly different between CABG and PCI (5,6).

To overcome this weakness of putting the same emphasis on individual components with a clinically different impact in the composite endpoint, a recent novel approach, the win ratio, has been introduced (7). Based on clinical priorities, the win ratio methodology applies a hierarchical weighting to individual components in MACCE. This approach is also designed to combat two fundamental difficulties that may be present in typical efficacy studies: study population heterogeneity and important events that are censored. The method uses risk score stratification to select and match pairs with similar risk profiles from both treatment groups and provides a more patient-specific interpretation of composite endpoints in clinical trials.

The objective of this re-analysis of the SYNTAX trial was to compare PCI with CABG using different methods of analysis, accounting for the severity of the individual components and prioritising these using the win ratio approach as an informative estimate of treatment difference. Moreover, this paper evaluates the impact of applying the win ratio on the design of future trials.

METHODS

Study design

The design and methods of the SYNTAX trial have been reported previously (8). In SYNTAX, 1,800 patients with *de novo* LM or three-vessel coronary artery disease were randomly assigned to undergo CABG or PCI with a paclitaxel-eluting stent (TAXUS® Express™; Boston Scientific, Marlborough, MA, USA). Patients with anticipated clinical revascularisation equipoise through PCI and CABG were randomised (CABG n=897, PCI n=903). Five year follow-up was 89.7% for CABG and 96.5% for PCI.

This study was carried out in accordance with the principles of the Declaration of Helsinki, and registered on the National Institutes of Health website with identifier NCT00114972.

Definitions

The primary endpoint of the trial was MACCE, which included all-cause death, stroke, MI, or repeat revascularisation (subsequent CABG or PCI) (9). Secondary endpoints consisted of: i) a composite safety endpoint of death/stroke/MI, and ii) the individual endpoint of all-cause death. Definitions of these endpoints have been published elsewhere (8). Medically treated diabetes was defined as treatment with oral hypoglycaemic agents or insulin at the time of enrolment.

Statistical analysis

All analyses were carried out according to the intention-to-treat principle. Conventional analyses were performed using: i) Cox proportional hazard analyses to provide hazard ratios (HRs), and ii) estimates of relative risk (RR) associated with PCI versus CABG treatment. The proportional hazards assumption was estimated using Schoenfeld's test and was found to have been met. Relative risks were calculated by dividing the Kaplan-Meier estimated rate of an event at five years in the PCI group by the event rate in the CABG group. The 95 percent confidence interval (CI) for the relative risk was calculated with the use of the standard errors from the Kaplan-Meier curve (10). The significance of differences in event rates between treatment groups was assessed with the use of the log-rank test. Conventional analyses were performed using SPSS software, Version 20.0 (IBM Corp., Armonk, NY, USA).

Win ratio analyses were performed for all-cause death, the composite safety endpoint of death/stroke/MI, and for the composite of MACCE (7). The hierarchy of events within MACCE was as follows: all-cause death, stroke, MI, repeat CABG, repeat PCI.

The win ratio can be used in a matched or unmatched fashion, depending on how the patients are compared. As recommended, priority was given to a matched approach versus an unmatched approach that dilutes the win ratio (7). In the matched approach, each patient in the CABG group was matched to a patient in the PCI group based on a similar risk of death. A risk score to predict death was developed using 18 pre-selected baseline variables that are known to be associated with prognosis (Table 1). A receiver operating characteristic (ROC) curve was generated to assess the ability of the scoring system model to predict mortality, 0.71 (95% CI: 0.67-0.75; p<0.0001). From the Cox proportional model's coefficients, a risk score was calculated for each patient in the trial. Patients in the two treatment groups formed matched pairs based on their risk profiles and ranks. For each pair, the new treatment is a "winner" or "loser" according to who had died first (Figure 1). If no deaths occurred, a "winner" or "loser" was designated based on who first had a stroke, and so forth using the hierarchy of events. If one patient had an event but the follow-up period of the matched patient was shorter or if there were pairs without an event, they were considered "tied". A "winner" patient had a more favourable outcome than his matched pair. The "win ratio" is the number of winners in the CABG group divided by the number of winners in the PCI group (Figure 1). An estimated win ratio >1 indicates a positive outcome of the CABG treatment compared to PCI while a win ratio <1 indicates a difference between treatment groups in favour of PCI. A corresponding 95% CI and p-values were calculated using dedicated statistical methods, as described by Pocock and co-authors (7).

Unmatched analyses were performed for subgroups according to diabetes, LM disease and SYNTAX score to compare this result with the matched approach. Due to the fact of unequal treatment groups in subgroups, some patients had to be excluded randomly to provide equal numbers for matching. In smaller subgroups within pre-specified subgroups of patients, up to 17% had to be excluded. To determine the impact of randomly excluding patients, a repeated analysis was performed 10 times to examine whether the obtained results were affected: this was performed in the subgroup of patients with LM disease and an intermediate SYNTAX score (n=190). The results of the 10 analyses were very different, with the win ratio ranging from 0.31-0.50 with p-values ranging from 0.0050-0.1052 for

all-cause death, and, respectively, 0.64-0.96 and 0.13-0.90 for MACCE. Therefore, only unmatched analyses were performed for the smaller SYNTAX score subgroups within subgroups of patients with LM/3VD and diabetes; no patients needed to be excluded for the unmatched analyses (11). In the unmatched approach, a CI for the win ratio cannot be directly calculated: the bootstrap method with 1,000 samples was performed to determine significance and CIs, using R software version 3.2.4 (Institute for Statistics and Mathematics of WU, Vienna, Austria). A p-value <0.05 was considered to be statistically significant for all analyses.

While originally the win-ratio code for unmatched analyses was designed for composite endpoints that include two components (death and re-hospitalisation), in order to analyse the SYNTAX trial data with five endpoints, the statistical code was rewritten, tested and validated according to the original statistical software provided directly by the authors of the win ratio approach (7), when we requested and as they recommended. Now, this code can be used to calculate the win ratio with any number of components in the composite endpoint (for the code contact e.andrinopoulou@erasmusmc.nl).

Table 1. Pre-selected variables for risk score model.

	Variable	Hazard ratio *p*-value*
Age	1.072	<0.001
Male sex	0.900	0.75
Body mass index	1.011	0.48
Current smoker	1.656	0.007
Medically treated diabetes	1.465	0.10
Previous myocardial infarction	1.370	0.030
Previous stroke	1.766	0.50
Previous transient ischaemic attack	0.825	0.80
Carotid artery disease	1.013	0.96
Congestive heart failure	1.166	0.88
Pulmonary hypertension	1.044	0.87
Peripheral vascular disease	2.513	<0.001
Creatinine >200 micromol/L	1.433	0.054
Dialysis	1.414	0.67
Chronic obstructive pulmonary disease	1.689	0.007
Ejection fraction moderate	1.405	0.040
Ejection fraction poor	1.371	0.006
SYNTAX score	1.010	0.093
Emergency treatment	0.707	0.58

**p*-value <0.05 is considered as statistically significant.

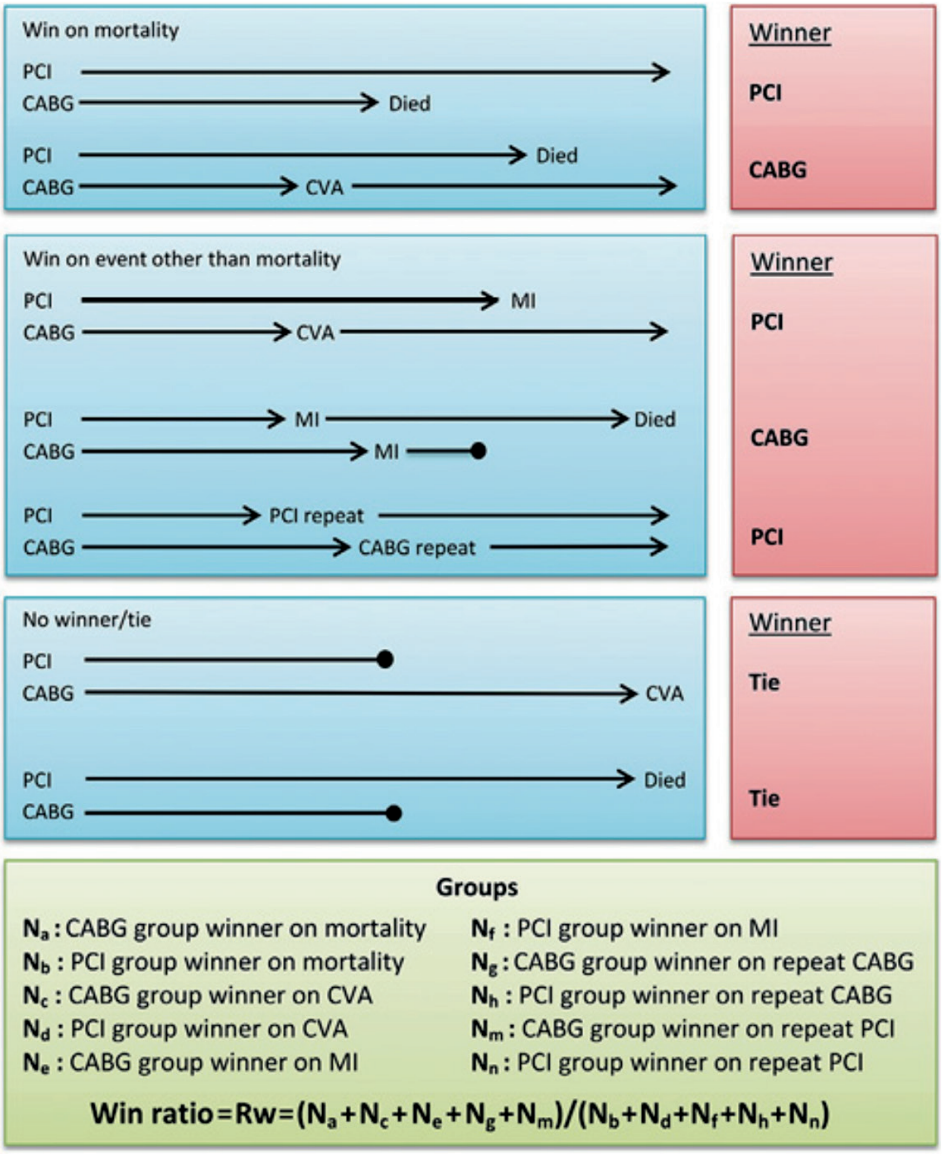


Figure 1. A conceptual diagram illustrating possible scenarios for the win ratio method. The determination of a "winner" is made using a predefined hierarchical outcome scheme. In the SYNTAX trial, mortality is considered the most important outcome followed by stroke, MI, repeat CABG revascularisation and repeat PCI revascularisation. The length of each arrow presents the duration of patient follow-up. Arrows ending in a solid circle denote either incomplete or shorter duration of follow-up.

RESULTS

Overall cohort

Of the 1,800 patients randomly assigned to PCI or CABG, 880 matched pairs were computed based on the risk score.

For the primary outcome of MACCE at five years, 274 patients who underwent CABG won versus 170 patients who underwent PCI, corresponding to a matched win ratio of 1.61 (95% CI: 1.341.96; p<0.0001) (Table 2, Figure 2). In comparison with matched analyses, unmatched analyses tended to have a smaller ratio between CABG and PCI (Figure 2).

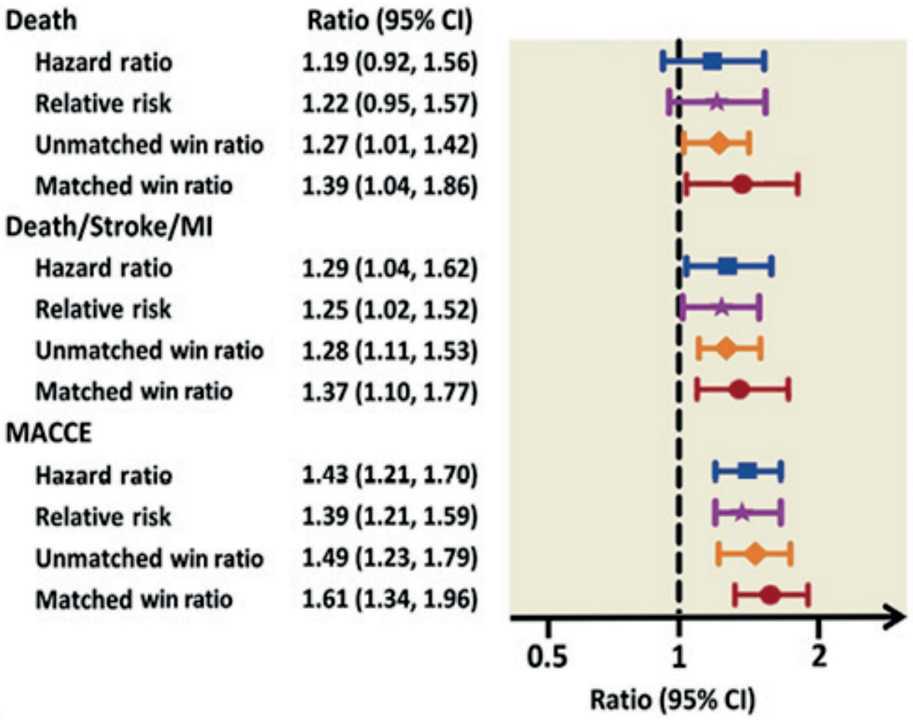


Figure 2. Win ratio approach vs. conventional analyses for the overall SYNTAX randomised cohort. Different colours represent conventional time-to-event hazard ratio analyses (blue), relative risk (purple), unmatched win ratio (orange), matched win ratio (red), approaches with 95% CIs. MACCE: major adverse cardiac and cerebrovascular events.

For the composite safety endpoint of death/stroke/MI, the win ratios and the conventional result were similar. The matched win ratio for the composite safety endpoint of death/stroke/MI was the analysis with the largest relative difference between CABG versus PCI in favour of CABG (n=116 vs. n=161, respectively; Rw=1.37, 95% CI: 1.10-1.77; p=0.006). Out of 578 (65.7%) matched pairs that were tied for the composite of death/stroke/MI, 552 pairs did not have an event of death/stroke/MI during follow-up, and 26 patients were tied because of a different length of follow-up (Table 2, Figure 2).

Table 2. The win ratio matched pairs approach, for the overall cohort and subgroups according to SYNTAX score terciles.

Matched pairs	SYNTAX trial	SYNTAX score ≤22	SYNTAX score 23-32	SYNTAX score ≥33
Death on PCI first	111	21	41	52
Death on CABG first	80	21	28	28
Stroke on PCI first	11	3	3	4
Stroke on CABG first	17	8	6	3
MI on PCI first	39	15	14	11
MI on CABG first	19	5	3	8
Repeat CABG on PCI first	24	9	10	9
Repeat CABG on CABG first	2	2	0	0
Repeat PCI on PCI first	89	29	27	29
Repeat PCI on CABG first	52	21	13	16
None of the above	437	137	149	127
Total number of pairs	880	272	294	287
Win ratio for MACCE	1.61	1.38	1.90	1.91
95% CI	1.34, 1.96	0.98, 1.87	1.37, 2.73	1.42, 2.75
Z-score	5.09	1.85	3.92	4.29
p-value	0.0001	0.064	0.0001	0.0001
Win ratio for death/stroke/MI	1.39	1.15	1.57	1.72
95% CI	1.10, 1.77	0.72, 1.83	1.05, 2.43	1.18, 2.62
Z-score	2.74	0.55	2.21	2.82
p-value	0.006	0.58	0.027	0.005
Win ratio for all-cause death	1.39	1.00	1.46	1.86
95% CI	1.04, 1.86	0.54, 1.86	0.92, 2.45	1.20, 3.07
Z-score	2.31	0	1.57	2.81
p-value	0.021	>0.99	0.12	0.005

CABG, coronary artery bypass grafting; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Death occurred first after CABG in 80 patients and first after PCI in 111 patients; the unmatched win ratio for all-cause death was 1.27 (95% CI: 1.01-1.42) and the matched win ratio was 1.39 (95% CI: 1.04-1.86), which was statistically significant unlike conventional analyses that resulted in an HR of 1.19 (95% CI: 0.92-1.56) (Table 2, Figure 2).

Subgroup analyses

SYNTAX score

In patients with intermediate and high SYNTAX scores, the matched win ratio for MACCE at five years confirmed statistically significant better outcomes with CABG (Rw=1.90, 95% CI: 1.37-2.73 and Rw=1.91, 95% CI: 1.42-2.75, respectively) (Figure 3, Table 2). Nevertheless, the magnitude of the treatment effect was larger with the matched win ratio; even in the group of patients with a low SYNTAX score, there was a trend towards a difference.

For the composite endpoint of death/stroke/MI, the matched win ratio increased significantly in favour of CABG from low to intermediate to high SYNTAX scores (Rw=1.15 vs. Rw=1.57 vs. Rw=1.72) as well as for all-cause death (Rw=1.00 vs. Rw=1.46 vs. Rw=1.86) (Figure 3, Table 2). However, the treatment effect of PCI versus CABG was strongest with the matched win ratio, and particularly for subgroups of patients with intermediate SYNTAX scores where there was a clear increase in the treatment effect. In comparison with conventional analyses, the findings from the unmatched analyses were similar in patients with low and high SYNTAX scores, but were stronger in favour of CABG for patients with intermediate SYNTAX scores (Figure 3).

LM/3VD

In patients with LM disease, the matched win ratio was not significantly different between CABG versus PCI: 1.27 (95% CI: 0.951.67) for MACCE, 1.02 (95% CI: 0.66-1.59) for the composite safety endpoint of death/stroke/MI, and 1.00 (95% CI: 0.70-1.44) for all-cause death (Figure 4, Table 3). In contrast, in patients with three-vessel disease, the matched win ratio for MACCE (Rw=1.92, 95% CI: 1.70-2.19), the composite safety endpoint of death/stroke/MI (Rw=2.00, 95% CI: 1.46-2.86), and all-cause death (Rw=2.15, 95% CI: 1.46-3.39) were all in favour of CABG. The unmatched approach supports the findings derived from conventional analyses in patients with LM, while unmatched analyses were stronger in favour of CABG among patients with three-vessel disease (Figure 4).

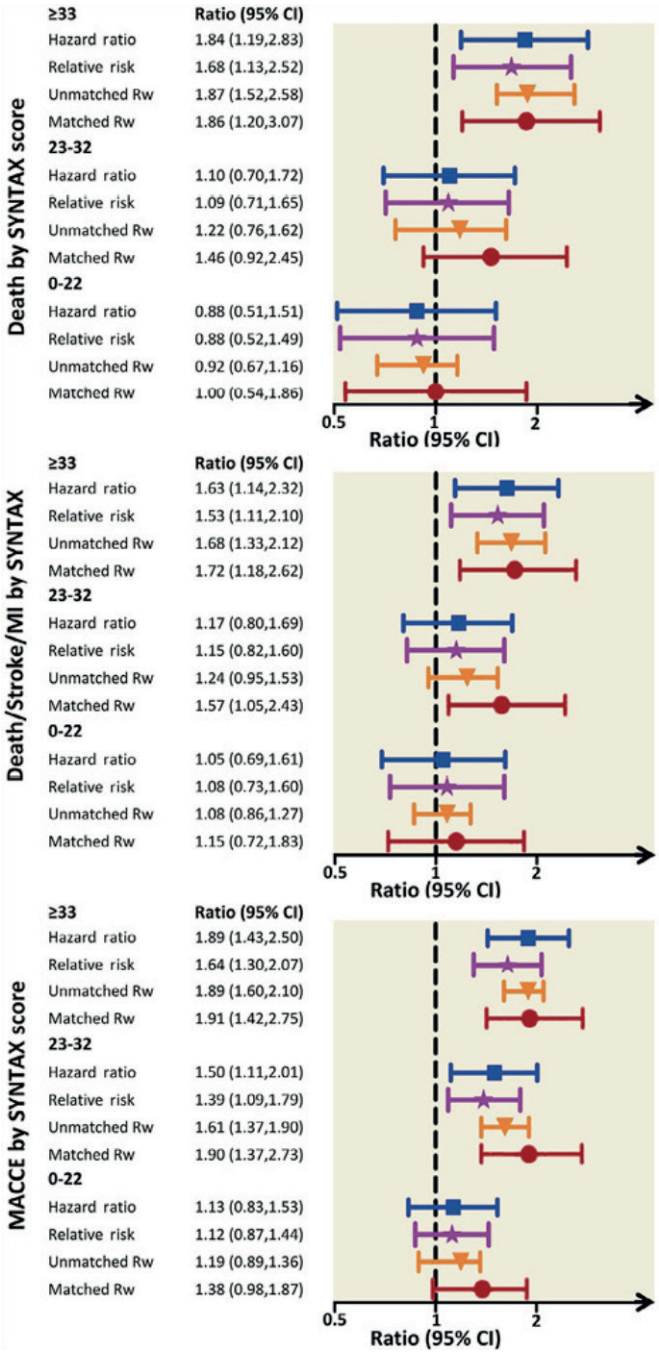


Figure 3. Win ratio approach vs. conventional analyses by baseline SYNTAX score terciles. MACCE, major adverse cardiac and cerebrovascular events.

When separately analysing SYNTAX score subgroups for MACCE, differences between conventional analyses, the unmatched analyses, and matched analyses were only minimal (Table 4). Of note, there was no consistency in changes in PCI versus CABG treatment effects choosing conventional or any win ratio analyses, although CIs appeared smaller when using win ratio analyses.

Table 3. The win ratio matched pairs approach, according to subgroups of left main disease and diabetes.

Matched pairs	Diabetes		Coronary disease	
	DM	Non-DM	3VD	LM
Death on PCI first	38	74	71	42
Death on CABG first	24	57	33	41
Stroke on PCI first	0	7	8	3
Stroke on CABG first	6	11	8	10
MI on PCI first	4	34	25	15
MI on CABG first	2	17	11	9
Repeat CABG on PCI first	8	19	10	8
Repeat CABG on CABG first	0	3	2	1
Repeat PCI on PCI first	72	62	57	35
Repeat PCI on CABG first	13	43	35	20
None of the above	95	336	278	152
Total number of pairs	217	663	538	336
Win ratio for MACCE	1.71	1.50	1.92	1.27
95% CI	1.19, 2.52	1.21, 1.88	1.70, 2.19	0.95, 1.67
Z-score	3.01	3.70	5.45	1.64
p-value	0.003	0.0002	<0.0001	0.10
Win ratio for death/stroke/MI	1.31	1.35	2.01	1.01
95% CI	0.83, 2.13	1.03, 1.81	1.46, 2.86	0.70, 1.44
Z-score	1.17	2.15	4.42	0
p-value	0.24	0.032	<0.0001	>0.99
Win ratio for all-cause death	1.59	1.30	2.15	1.02
95% CI	0.96, 2.70	0.92, 1.86	1.46, 3.39	0.66, 1.59
Z-score	1.82	1.50	4.01	0.11
p-value	0.069	0.13	<0.001	0.91

CABG, coronary artery bypass grafting; CI, confidence interval; DM, medically treated diabetes; LM, left main coronary disease; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; 3VD, three-vessel disease.

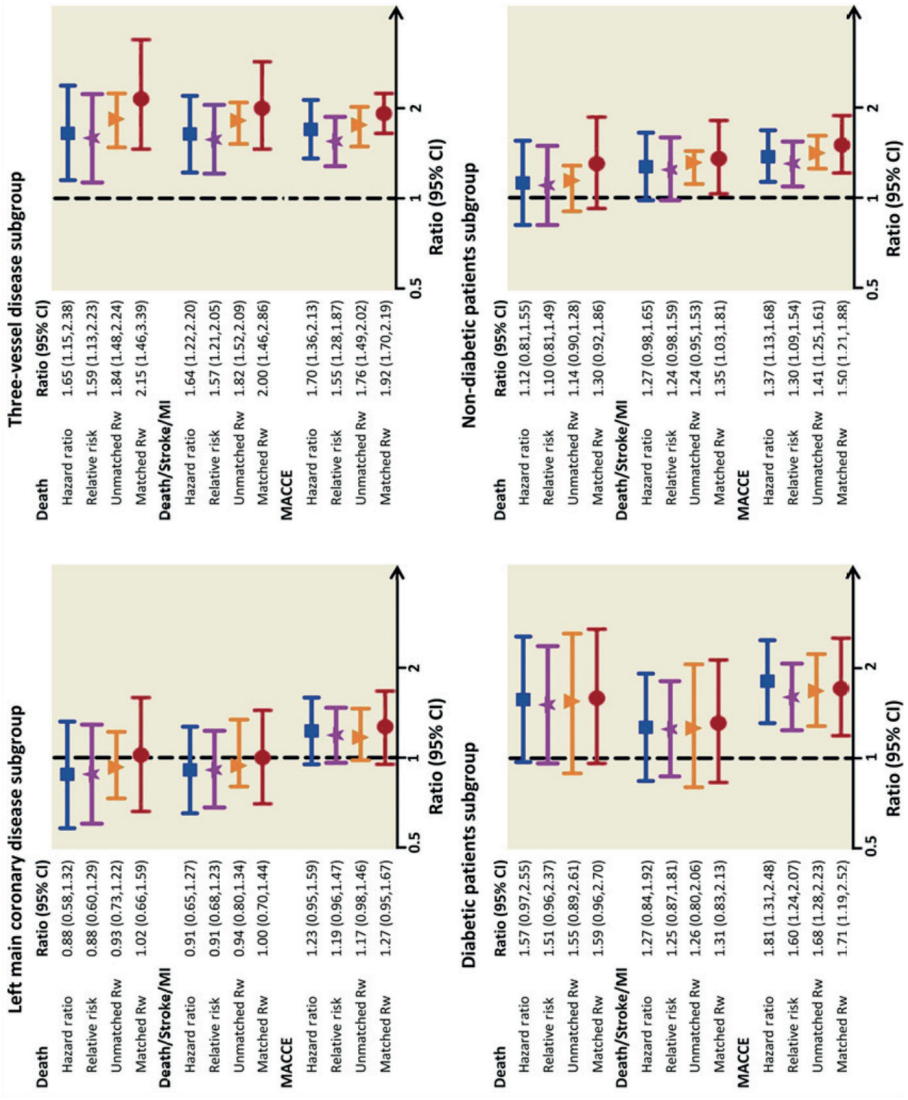


Figure 4. Win ratio approach vs. conventional analyses by baseline subgroups. MACCE, major adverse cardiac and cerebrovascular events.

Diabetes

In diabetic as well as non-diabetic patients, results using matched and unmatched win ratio approaches were comparable to those from conventional analyses (Figure 4, Table 3). In diabetic patients, MACCE was significantly lower in favour of CABG with a matched win ratio of 1.71 (95% CI: 1.19-2.52; p=0.003), while all-cause death and the composite of death/stroke/MI were not significantly different between CABG and PCI. In non-diabetic patients, results with the matched win ratio approach slightly favoured CABG in comparison to conventional analyses, although these differences were minimal.

In separate analyses applying the unmatched win ratio approach to SYNTAX score terciles, the overall results of diabetics and nondiabetics were consistent with conventional analyses (Table 4). There was no consistency in increasing or decreasing the treatment effect of PCI versus CABG when using the win ratio approach.

Table 4. Unmatched win ratio approach for MACCE, according to subgroups of SYNTAX score within LM/3VD and diabetic subgroups.

SYNTAX score	Type of analysis	Left main disease	Three-vessel disease	Diabetes	Non-diabetes
0-22	Hazard ratio	0.91 (0.56, 1.47)	1.28 (0.87, 1.90)	1.30 (0.74, 2.28)	1.03 (0.71, 1.47)
	Relative risk	0.96 (0.64, 1.44)	1.24 (0.89, 1.73)	1.26 (0.81, 1.97)	1.06 (0.77, 1.45)
	Unmatched Rw	0.93 (0.74, 1.89)	1.28 (1.02, 1.63)	1.26 (0.87, 2.58)	1.08 (0.95, 1.21)
23-32	Hazard ratio	0.94 (0.57, 1.55)	1.88 (1.29, 2.72)	1.56 (0.94, 2.64)	1.48 (1.07, 2.06)
	Relative risk	1.01 (0.67, 1.52)	1.68 (1.22, 2.31)	1.45 (0.92, 2.30)	1.38 (1.02, 1.85)
	Unmatched Rw	0.87 (0.55, 1.20)	1.83 (1.38, 2.87)	1.45 (0.80, 2.11)	1.41 (1.01, 2.11)
≥33	Hazard ratio	1.78 (1.21, 2.63)	2.02 (1.35, 3.03)	2.25 (1.51, 4.30)	1.62 (1.16, 2.25)
	Relative risk	1.57 (1.15, 2.14)	1.74 (1.24, 2.44)	2.22 (1.43, 3.45)	1.46 (1.11, 1.91)
	Unmatched Rw	1.68 (1.46, 2.27)	2.11 (1.62, 3.03)	2.70 (1.64, 2.89)	1.61 (1.20, 2.12)

Results are displayed as ratios with 95% CI between brackets. Rw, win ratio.

DISCUSSION

The current analysis demonstrates that, by hierarchically prioritising events in the composite of MACCE, the treatment effect of CABG versus PCI is larger than with conventional analyses. In smaller subgroups of patients, for which unmatched win ratio analyses are necessary, differences between the win ratio approach and conventional analyses are minimal. These results provide additional insights into the SYNTAX trial results and have several important implications for future trial conduct.

PCI versus CABG

The use of composite endpoints in trials is problematic because it may provoke controversy regarding their suitability (12). Components are often unreasonably combined (12,13), results are difficult to interpret (14-16), and favourable outcomes or combinations of outcomes are cherry picked (6,17). The criticism of the PCI versus CABG trials is that the superiority of CABG is primarily driven by repeat revascularisation which has less of a clinical impact than all-cause death, stroke and MI (5). When repeat revascularisation is not part of the composite endpoint, there is no statistically significant difference between PCI and CABG in many trials. A meta-analysis of four trials comparing PCI with stents versus CABG also did not show a difference in rates of death/stroke/MI between CABG and PCI (18). However, overall MACCE rates at five years were significantly lower in CABG patients as a result of persistently lower repeat revascularisation rates in those patients (18).

The win-ratio approach addresses the limitations of softer clinical components in a composite endpoint by putting more emphasis on events with greater clinical importance. The win-ratio analysis takes into account not only the number of events, but also the timing of the event. While there was no statistically significant difference in survival at longest follow-up in the SYNTAX study, the Kaplan-Meier curves showed a continuous higher all-cause mortality rate after PCI. In a conventional time-to-event analysis with log-rank testing, this difference is not reflected. The win-ratio analysis of the SYNTAX trial shows that the benefit of CABG over PCI is evident in terms of both lower MACCE and lower all-cause mortality rates (p=0.021). Using the win ratio, this is the first time that a difference in all-cause mortality between PCI and CABG has been shown.

In patients with low SYNTAX scores, the win ratio for MACCE was not statistically different between treatment groups, but there was a considerable difference between the win-ratio and conventional analysis, suggesting that CABG may be favourable even in this subgroup of patients with a low SYNTAX score. This can be explained by the three times higher MI rates and the necessity for repeat CABG revascularisation in the PCI group. However, these findings are hypothesis-generating, and the preferred revascularisation method in the group with a low SYNTAX score remains a matter of debate that will need evaluation in future clinical trials.

Future clinical trial design

The win ratio proves to be an important method for analysing future randomised clinical trial data. The unmatched win ratio substantially increases statistical power, while the matched win ratio showed an even larger increase in treatment effect (19,20). Using the win ratio for sample size calculations may therefore reduce the number of patients in a trial, with the obvious advantages of shorter enrolment and lower costs. Expanding the number of components and including components with a wide range of impact severity will increase event rates and reduce the sample size further. While this would be considered inappropriate for conventional analyses (21), this is not an issue when applying the win ratio since events are prioritised based on their impact severity.

When using the win ratio, however, it is important to alternate between the matched and unmatched approaches. Although the matched approach is favoured, our subgroup analysis that was performed 10 times suggests that exclusion of patients from an analysis in order to produce matched pairs can create a selection bias, causing an incorrect estimate of the true treatment effect on the outcome of interest. Therefore, it is recommended to use the unmatched approach when matching two treatment groups for which a substantial number of patients (arbitrarily >10%) should be excluded for matching.

STUDY LIMITATIONS

Applying the win ratio has some limitations. First, there is no clear consensus on ranking the severity of the events in MACCE. In this study, we used the weighting scheme as proposed by Tong and coauthors (17). In addition, a repeat CABG was rated as having more impact than repeat PCI. One may also argue that repeat CABG may have more impact than MI, due to its invasiveness and potential complications. Secondly, even within a single event, there are different degrees of severity, such as major MI with subsequent left ventricular dysfunction versus MI in the smaller branches of the coronary arteries, with less impact on a patient's quality of life and prognosis. Likewise, a severe MI may have more consequences than a minor stroke. Future validation and verifications of the win ratio should be conducted before it becomes widely used in clinical trials. Moreover, the use of TAXUS stents in clinical practice was superseded by second-generation DES, which has been shown to improve long-term outcomes significantly. Therefore, the presented analyses must be considered observational and "hypothesis-generating".

It should be acknowledged that a hazard ratio (HR), relative risk (RR) and the win ratio (Rw) are different outcome measures, and it is therefore unclear whether they can be compared directly.

CONCLUSIONS

The win ratio is a new method to analyse composite endpoints within clinical trials. It can be used effectively and provides a stronger estimate of a treatment effect than conventional analyses. Furthermore, it can easily be extended to analyse composite endpoints with multiple components and with a wider range of impact severity, while maintaining integrity. Based on these advantages, future trials adopting this approach can expect similar statistical power with smaller sample sizes, and lower trial costs.

In case of PCI versus CABG in the SYNTAX trial, this re-analysis bolstered the results of the conventional analysis and strengthened the finding in favour of CABG treatment for patients with complex coronary disease. This provides evidence that hard clinical outcomes in particular (e.g., death and MI) after CABG are less frequent as compared with PCI. It is important to emphasise that this analysis does not undermine the findings of the original conventional analysis based on a traditional pre-specified design; it does, however, more appropriately estimate the treatment effect of PCI versus CABG by prioritising hard clinical endpoints over softer endpoints.

IMPACT ON DAILY PRACTICE

This study demonstrates that the win ratio approach can be simply and efficiently used to analyse composite outcomes in clinical trials that have combined several components with different clinical importance into a single measure. The obtained results provide a valuable framework to clinicians for meaningful outcome analysis following percutaneous coronary intervention and coronary artery bypass grafting. The win ratio has several advantages over conventional analyses and may be pre-specified in future trial designs.

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Chapter 12

The impact of chronic kidney disease on outcomes following percutaneous coronary interventions versus coronary artery bypass grafting in patients with complex coronary artery disease: 5-year follow-up of the SYNTAX trial

Milojevic M, Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD, Holmes DR Jr, Serruys PW, Kappetein AP.

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ABSTRACT

AIMS: The aim of this study was to investigate short-term and five-year follow-up results from patients randomised to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with paclitaxel-eluting stents in the SYNTAX trial, focusing on patients with chronic kidney disease (CKD).

METHODS AND RESULTS: Baseline glomerular filtration rate estimates (eGFR) were available in 1,638 patients (PCI=852 and CABG=786). The Kidney Disease: Improving Global Outcomes (KDIGO) threshold was used to define staging of CKD. At five years, death was significantly higher in patients with CKD compared to patients with normal kidney function after PCI (26.7% vs. 10.8%, p<0.001) and CABG (21.2% vs. 10.6%, p=0.005). Comparing PCI with CABG, there was a significant interaction according to kidney function for death (p_{int}=0.017) but not the composite endpoint of death/stroke/MI (p_{int}=0.070) or MACCE (p_{int}=0.15). In patients with CKD, the rate of MACCE was significantly higher after PCI compared with CABG (42.1% vs. 31.5%, p=0.019), driven by repeat revascularisation (21.9% vs. 8.9%, p=0.004) and allcause death (26.7% vs. 21.2%, p=0.14). In patients with CKD who also had diabetes, PCI versus CABG was significantly worse in terms of death/stroke/MI (47.9% vs. 24.4%, p=0.005) and all-cause death (40.9% vs. 17.7%, p=0.004).

CONCLUSIONS: During a five-year follow-up, adverse event rates were comparable between PCI and CABG patients with moderate CKD but significantly higher compared to the patients with impaired or normal kidney function. The negative impact of CKD on long-term outcome following PCI appears to be stronger when compared to CABG, especially in the CKD patients with diabetes and extensive coronary disease.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide healthcare problem with an increasing incidence (1). Despite the magnitude of resources committed to its treatment, CKD is one of the leading causes of death in Western countries (2). End-stage renal disease, but also the early stages of CKD are found to be strong independent predictors of developing coronary artery disease (CAD) with subsequently markedly increased rates of cardiovascular events and high mortality (3). The high prevalence of diabetes among patients with CKD contributes to the progression of renal disease, thereby promoting accelerated atherosclerosis that results in diffuse coronary artery calcifications and represents a group at high risk of cardiac mortality (4). It remains unclear whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be preferred in patients with CKD. According to the 2014 ESC/EACTS guidelines on myocardial revascularisation, CABG is preferable over PCI in patients with CKD if the life expectancy is more than one year, while PCI is recommended in patients with a life expectancy of less than one year. However, the current guidelines are based on observational studies with inherent limitations (5,6). A subgroup analysis of the ARTS trial provides data from a randomised comparison of CABG with PCI using bare metal stents (BMS) in patients with CKD, but these results are difficult to interpret in the current DES era (7). Moreover, data on the optimal revascularisation strategy in patients with a combined disease burden of CKD and diabetes are only available from the FREEDOM trial in which the authors were unable to report any differences among diabetic/nondiabetic patients because the population consisted only of diabetic patients with CKD, as mentioned in their limitations (8).

In the SYNTAX trial, PCI with first-generation paclitaxel-eluting stents was compared with CABG for patients with *de novo* three-vessel and/or left main (LM) disease. Unlike previous trials (9), patients with CKD were not routinely excluded (10). Therefore, this study presents unique data of patients with CKD by comparing five-year outcomes between CABG and PCI along the spectrum of kidney function.

METHODS

Study design

The SYNTAX trial design and methods have been described previously (10). Briefly, SYNTAX was a prospective, multinational, randomised clinical trial in which 1,800 patients were randomly assigned to undergo PCI with first-generation paclitaxel-eluting stents (TAXUS™ Express™; Boston Scientific, Marlborough, MA, USA) or CABG. Patients were randomly assigned in a 1:1 fashion to undergo PCI (n=903) or CABG (n=897).

This study was carried out according to the principles of the Declaration of Helsinki. The trial is registered with number NCT00114972 at the ClinicalTrials.gov website.

Definitions and endpoints

The definitions used for the classification of adverse events have been reported previously (10,11). The primary endpoint of the SYNTAX trial was the composite rate of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, stroke, myocardial infarction (MI), and repeat revascularisation. Secondary endpoints in this study included the composite safety endpoint of death/stroke/MI and rates of the individual MACCE components.

Estimation of the glomerular filtration rate (eGFR) was used to assess the degree of kidney failure. The eGFR was calculated from the baseline serum creatinine level, which was available in 1,638 patients (PCI=852, 94.3% and CABG=786, 87.6%). Of the remaining 162 (9.0%) patients, the baseline creatinine could not be determined (Supplementary Table 1). For each patient, the eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (12). The Kidney Disease: Improving Global Outcomes (KDIGO) threshold was used to define the CKD population (13). According to KDIGO classifications, patients were classified according to the eGFR: stage 1, patients with a normal kidney function had an eGFR of ≥90 mL/min per 1.73 m^2; stage 2, impaired renal function, defined by an eGFR between 60 and 89 mL/min per 1.73 m^2; and stages 3-5, CKD, defined by an eGFR <60 mL/min per 1.73 m^2. Patients with CKD were further subdivided into stage 3 (eGFR 30-59 mL/min per m^2), stage 4 (eGFR 15-29 mL/min per 1.73 m^2) and stage 5 (chronic dialysis treatment) (13). Using these classifications, the following subgroups were defined and analysed in the current study: i) normal kidney function (stage 1); ii) impaired kidney function (stage 2); and iii) CKD (stages 3, 4 and 5), the latter being pooled together into a single group due to the low number of patients in stages 4 and 5 subgroups.

Statistical analysis

Data are presented using descriptive statistics, as a percentage, count of sample size, or mean±standard deviation (SD). Either the Student's t-test or the Kruskal-Wallis test was used to compare continuous variables. Differences in discrete variables were compared with a χ^2 or Fisher's exact test, where appropriate.

All analyses were based on the intention-to-treat principle. Short-term outcomes were defined within 30 days after the procedure. Five-year rates of adverse events were estimated using the Kaplan-Meier method, and comparisons between groups were made using log-rank tests. P-values for interaction were acquired using a logistic regression chi-square test. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) with PCI as the reference group. The proportionality for Cox models was tested with Schoenfeld residuals and confirmed no significant departures from the proportionality assumption. A two-sided p-value of <0.05 was considered to be statistically significant. Analyses were performed using SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 1,638 patients, only 219 (25.7%) patients randomised to PCI and 209 (26.6%) patients randomised to CABG had a normal kidney function (Figure 1). The majority of patients had impaired kidney function (PCI=475 (55.8%) and CABG=426 (54.2%)), whereas CKD was present in 158 (18.5%) patients randomised to PCI and 151 (19.2%) patients randomised to CABG. Among patients with CKD, 24 patients (PCI=13 (8.2%) and CABG=11 (7.3%)) had severe CKD (stage 4) and six patients (PCI=3 (1.9%) and CABG=3 (2.0%)) were on chronic dialysis (stage 5). Patients without information on GFR had similar baseline characteris tics and five-year outcomes to patients with information on GFR (Supplementary Table 1).

Patient characteristics

The risk profile of patients was comparable between PCI and CABG in all categories of patients (Supplementary Table 2). Patients with CKD (mean eGFR 47.6±10.8 mL/min/1.73 m^2) had a markedly higher risk profile at baseline than patients with normal or impaired kidney function, reflecting an overall higher logistic EuroSCORE. There were no differences regarding baseline coronary disease complexity as determined by the SYNTAX score (Table 1, Supplementary Table 3). However, a subgroup of CKD patients with diabetes had a significantly higher SYNTAX score compared to non-diabetic CKD patients (32.2±12.1 vs. 28.2±11.7, p=0.008).

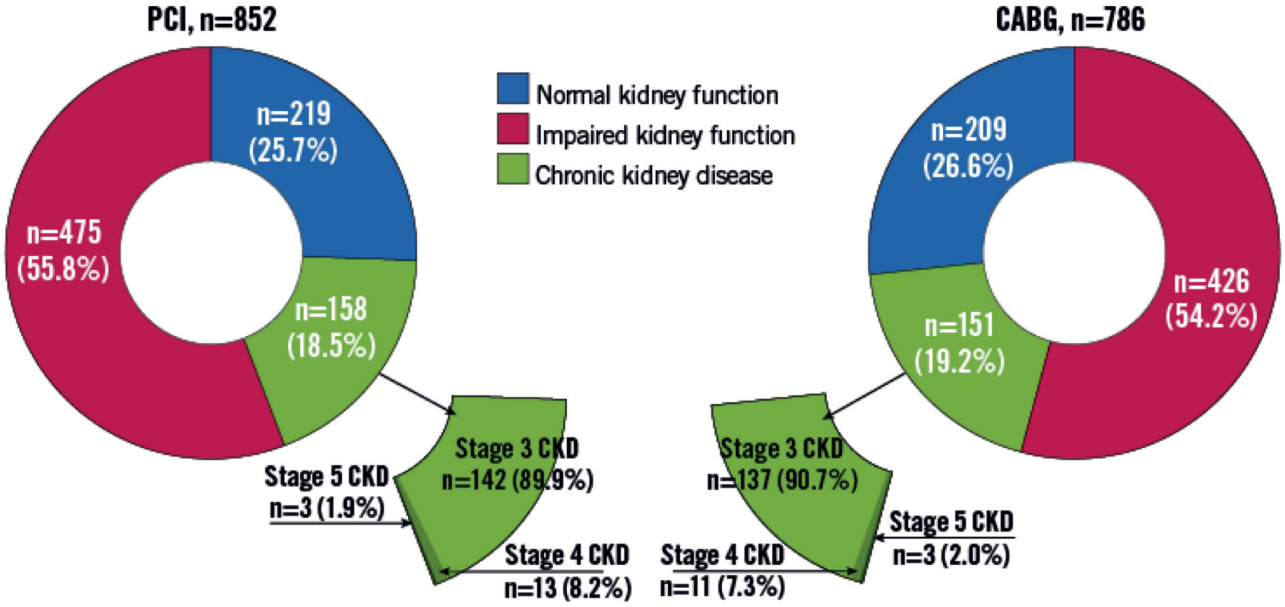


Figure 1. *Distribution of patients enrolled in the SYNTAX randomised cohort according to kidney function. Groups consist of patients with normal kidney function as defined by an eGFR ≥90 mL/min per 1.73 m*^{2}*, impaired kidney function as defined by an eGFR=60-89 mL/min per* 1.73 m^2, and chronic kidney disease as defined by an eGFR <60 mL/min per 1.73 m^2. The group of patients with CKD includes patients in stage 3 CKD as defined by an eGFR=30-59 mL/min per 1.73 m^2, stage 4 CKD as defined by an eGFR=15-29 mL/min per 1.73 m^2, and stage 5 CKD as defined by an eGFR <15 mL/min per 1.73 m^2. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Table 1. Baseline characteristics of patients and 30-day outcomes by kidney function within PCI and CABG randomised cohorts.

	PCI cohort				CABG cohort			
	Normal kidney function (n=219)	Impaired kidney function (n=475)	CKD (n=158)	*p*-value	Normal kidney function (n=209)	Impaired kidney function (n=426)	CKD (n=151)	*p*-value
Age, years	58.8±9.4	66.0±8.7	71.9±7.3	<0.001	59.3±9.9	65.3±8.8	71.6±7.9	<0.001
Male	174 (79.5)	372 (78.3)	108 (68.4)	0.020	173 (82.8)	353 (82.9)	101 (66.9)	<0.001
Medically treated diabetes	46 (21.0)	129 (27.2)	44 (27.8)	0.18	51 (24.4)	88 (20.7)	50 (33.1)	0.009
Peripheral vascular disease	19 (8.7)	38 (8.0)	21 (13.3)	0.13	13 (6.2)	47 (11.0)	24 (15.9)	0.013
Hypertension	144 (66.1)	343 (72.8)	135 (86.0)	<0.001	155 (74.9)	308 (72.6)	128 (85.3)	0.007
Hyperlipidaemia	164 (75.2)	376 (79.8)	122 (77.7)	0.39	166 (79.8)	321 (76.4)	119 (79.3)	0.56
Carotid artery disease	9 (4.1)	39 (8.2)	19 (12.0)	0.017	10 (4.8)	29 (6.8)	25 (16.6)	<0.001
Previous MI	74 (34.1)	140 (29.9)	58 (36.9)	0.21	84 (40.2)	133 (31.6)	47 (32.0)	0.085
LVEF poor (<30%)	2 (0.9)	5 (1.1)	3 (1.9)	0.64	3 (1.4)	8 (1.9)	8 (5.3)	0.035
SYNTAX score	27.4±11.2	28.5±11.3	29.6±12.3	0.18	28.8±11.7	29.5±11.2	29.3±11.7	0.79
30-day outcomes								
MACCE	14 (6.4)	24 (5.1)	10 (6.3)	0.70	12 (5.8)	18 (4.2)	6 (4.0)	0.63
Death/stroke/MI	11 (5.0)	20 (4.2)	9 (5.7)	0.71	10 (4.8)	17 (4.0)	4 (2.6)	0.58
Death, all-cause	4 (1.8)	8 (1.7)	4 (2.5)	0.78	2 (1.0)	2 (0.5)	1 (0.7)	0.76
Repeat revascularisation	8 (3.7)	15 (3.2)	3 (1.9)	0.62	4 (1.9)	5 (1.2)	2 (1.3)	0.75

Values are presented as mean±SD or n/N (%). Kaplan-Meier event rates were estimated at 30 days with p-values from log-rank test. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MACCE, major adverse cardiac and cerebrovascular events; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Procedural characteristics and discharge medication

Off-pump CABG was performed more often in patients with CKD compared to patients with impaired or normal kidney function (22.1% vs. 13.1% vs. 15.8%, respectively; p=0.035) (Supplementary Table 4). The use of multiple arterial grafts was lower in CKD patients; in particular, bilateral internal mammary arteries (BIMA) were used less frequently (18.8% vs. 28.5% vs. 34.2%, respectively; p=0.007). The number of distal anastomoses and the completeness of revascularisation did not differ between groups.

In the PCI group, there were no differences among the groups in the procedural aspect regarding stent use (Supplementary Table 4). However, the rate of complete revascularisation was substantially lower in patients with CKD versus those with impaired kidney function or normal kidney function (46.2% vs. 60.5% vs. 56.5%, respectively; p=0.007), while a comparable number of patients underwent staged procedures (14.6% vs. 12.0% vs. 17.4%, respectively; p=0.16). Acetylsalicylic acid was prescribed less often in patients with CKD compared to patients with impaired kidney function or normal kidney function after PCI (93.0% vs. 96.4% vs. 99.1%, respectively; p=0.006) and CABG (83.0% vs. 89.2% vs. 91.7%, respectively; p=0.043) (Supplementary Table 4). No differences in the administration of statins and beta-blockers were found in either treatment group. In general, secondary preventive medication was prescribed more often after PCI than after CABG (Supplementary Table 2).

Short-term outcomes

Within the PCI and CABG groups, incidences of 30-day adverse events were comparable in patients with CKD, impaired kidney function, and normal kidney function (Table 1). Comparing outcomes between PCI and CABG in patients with CKD, there were no significant differences in rates of MACCE (6.3% vs. 4.0%, respectively, p=0.34), the composite of death/stroke/MI (5.7% vs. 2.6%, respectively, p=0.18), all-cause death (2.5% vs. 0.7%, respectively, p=0.19), or repeat revascularisation (1.9% vs. 1.3%, respectively, p=0.68) (Supplementary Table 2).

Five-year outcomes

In separate groups of both PCI and CABG, rates of adverse events were not significantly different between patients with normal vs. impaired kidney function, while patients with CKD vs. normal kidney function had significantly higher rates of MACCE, the composite safety endpoint of death/stroke/MI, and all-cause death (Supplementary Table 5). Rates of repeat revascularisation were lower in patients with impaired kidney function and CKD.

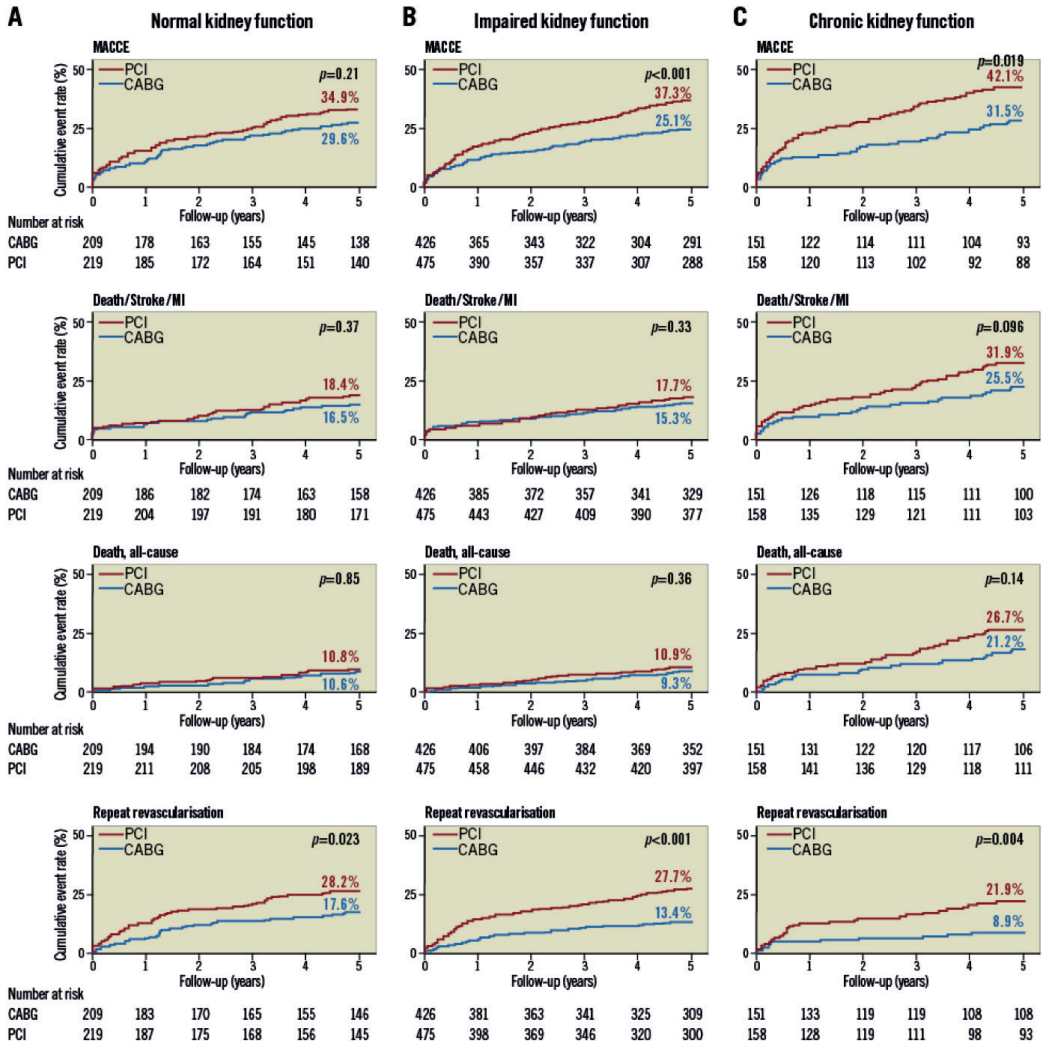


Figure 2. Kaplan-Meier cumulative event curves by the status of kidney function in the SYNTAX randomised cohort. p-values are from log-rank test. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Outcomes at 5 years stratified by baseline kidney function.

	PCI	CABG	HR (95% CI)	*p*-value
Normal kidney function	n=219	n=209		
MACCE	73 (34.9)	56 (29.6)	1.25 (0.88-1.77)	0.21
Death/stroke/MI	40 (18.4)	30 (16.5)	1.24 (0.77-1.99)	0.37
Death, all-cause	21 (10.8)	18 (10.6)	1.06 (0.57-2.00)	0.85
Repeat revascularisation	57 (28.2)	34 (17.6)	1.63 (1.06-2.49)	0.023
Impaired kidney function	n=475	n=426		
MACCE	174 (37.3)	102 (25.1)	1.60 (1.25-2.04)	<0.001
Death/stroke/MI	83 (17.7)	62 (15.3)	1.18 (0.85-1.63)	0.33
Death, all-cause	51 (10.9)	37 (9.3)	1.22 (0.80-1.86)	0.36
Repeat revascularisation	125 (27.7)	53 (13.4)	2.25 (1.63-3.10)	<0.001
CKD	n=158	n=151		
MACCE	66 (42.1)	42 (31.5)	1.58 (1.08-2.33)	0.019
Death/stroke/MI	50 (31.9)	33 (25.5)	1.45 (0.93-2.25)	0.096
Death, all-cause	41 (26.7)	27 (21.2)	1.44 (0.88-2.34)	0.14
Repeat revascularisation	31 (21.9)	12 (8.9)	2.56 (1.31-4.99)	0.004

Values are presented as n/N (%). Data are Kaplan-Meier estimates of adverse events with *p*-values from log-rank test. Treatment-by-kidney status interactions failed to reach statistical significance for MACCE (p_{int}=0.15), the composite safety endpoint (p_{int}=0.070), all-cause death (p_{int}=0.017), and repeat revascularisation (p_{int}=0.65). CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

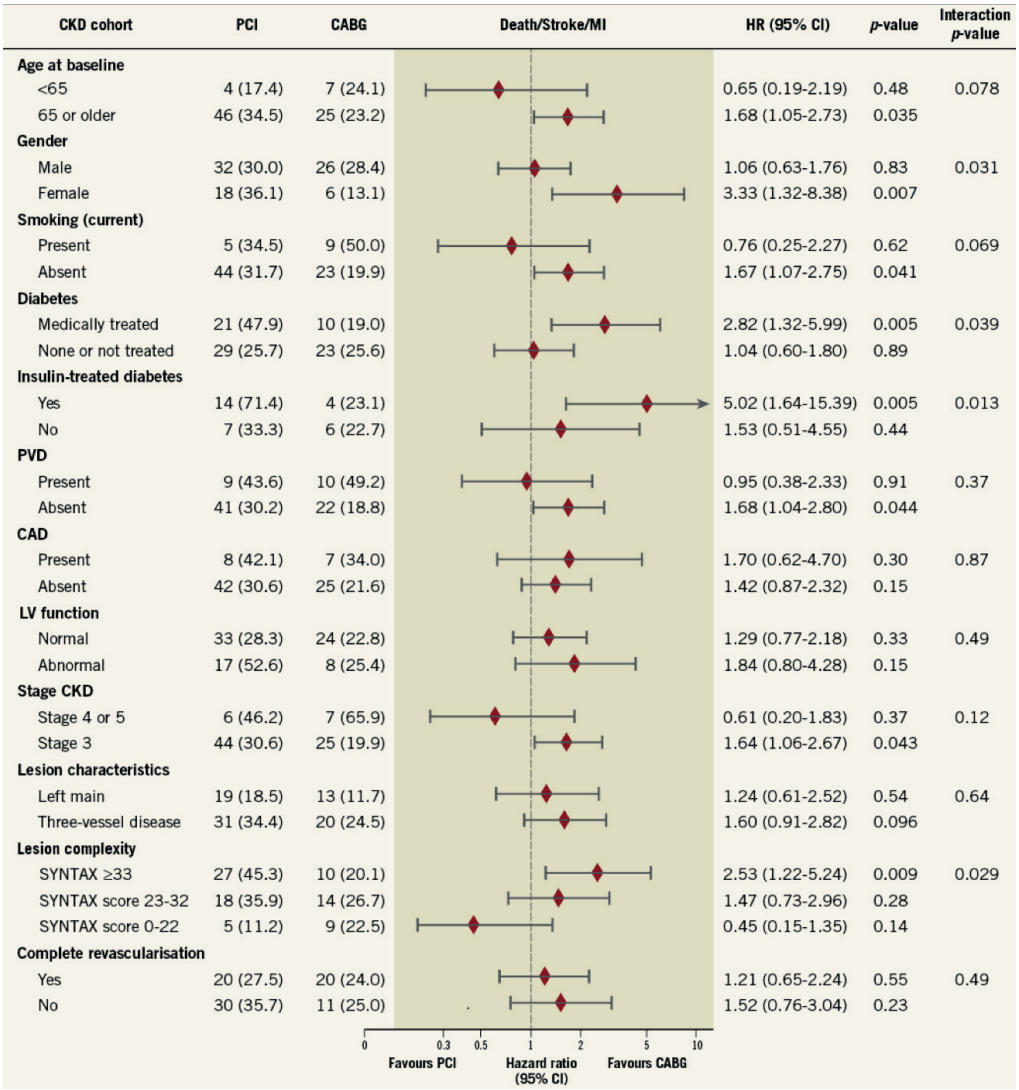


Figure 3. Hazard ratios of PCI versus CABG according to subgroups based on patient characteristics by the status of kidney function. Values are Kaplan-Meier event rates at five years with p-values from log-rank test. CABG, coronary artery bypass grafting; CAD, carotid artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Overall, differences between PCI and CABG in rates of adverse events were larger in patients with CKD than in other groups (Table 2, Supplementary Table 6, Figure 2). There was a significant treatment-by-kidney function interaction for all-cause death (p_{int}=0.017), while interactions for MACCE (p_{int}=0.15) or the composite endpoint of death/stroke/MI (p_{int}=0.070) did not reach statistical significance.

In patients with CKD, the rate of MACCE was significantly higher after PCI than after CABG (42.1% vs. 31.5%, respectively; p=0.019) (Table 2, Figure 2). Rates of the composite endpoint of death/stroke/MI were 31.9% vs. 25.5%, respectively (p=0.096), and for all-cause death 26.7% vs. 21.2%, respectively (p=0.14).

Subgroup analysis

The rates of the composite of death/stroke/MI were significantly lower in patients with normal or impaired kidney function compared to CKD patients irrespective of the patient's baseline characteristics (Supplementary Figure 1).

Overall, subgroup analyses among patients with CKD demonstrated a largely consistent benefit of CABG over PCI (Figure 3). However, significant interactions were found for gender, SYNTAX score and diabetes.

Subgroup analyses according to diabetic status show a persistent increase in the difference in adverse events between CABG and PCI with increasing kidney failure (from normal kidney function to CKD) (Supplementary Table 7). Among CKD groups, nondiabetic patients had comparable rates between PCI and CABG regarding the composite of death/stroke/MI (HR 1.04, 95% CI: 0.60-1.80; p=0.89) and all-cause death (HR 0.94, 95% CI: 0.511.71; p=0.83) (Figure 4). In contrast, diabetic patients assigned to PCI compared to CABG had significantly higher rates of the composite of death/stroke/MI (HR 2.82, 95% CI: 1.32-5.99; p=0.005 with p_{int}=0.039) and all-cause death (HR 3.39, 95% CI: 1.41-8.13; p=0.004 with p_{int}=0.018) (Figure 4).

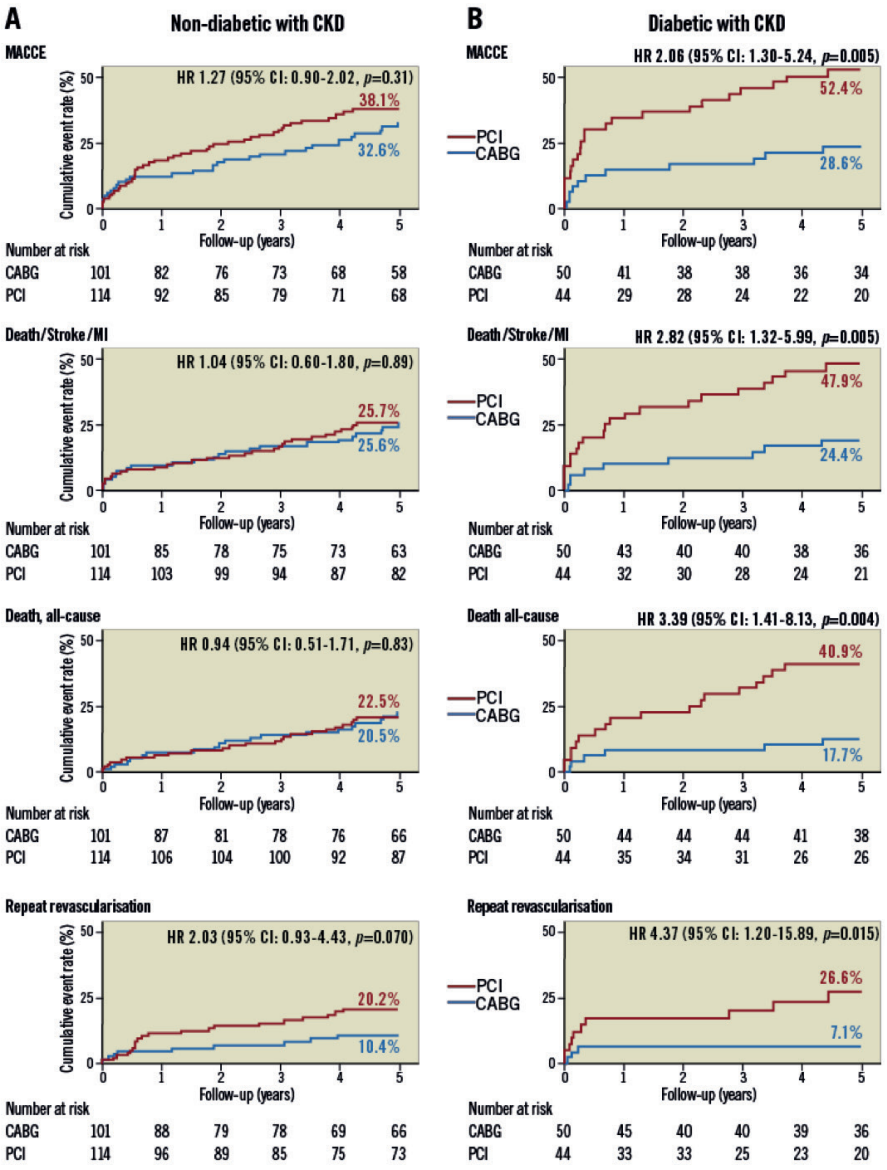


Figure 4. Kaplan-Meier cumulative event curves in patients with chronic kidney disease stratified by medically treated diabetes in the SYNTAX randomised cohort. Curves are separated for **(A)** non-diabetic patients and **(B)** medically treated diabetic patients. Treatment-by-diabetes interactions: MACCE (p_{int}=0.10), the composite safety endpoint (p_{int}=0.039), all-cause death (p_{int}=0.018) and repeat revascularisation (p_{int}=0.39). p-values are from log-rank test. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

DISCUSSION

This five-year analysis of the SYNTAX trial provides unique data on patients with and without CKD undergoing revascularisation. Important findings are that: i) the treatment plan for patients with versus without CKD differed significantly with CABG (e.g., less BIMA and more off-pump) and PCI (e.g., less complete revascularisation); ii) patients with CKD suffer from receiving less guideline-directed secondary prevention; iii) patients with CKD have significantly poorer outcomes after both PCI and CABG than patients with normal or impaired kidney function; and iv) differences in the five-year adverse event rates between PCI and CABG were minimal in patients with a normal kidney function but in favour of CABG in patients with CKD, particularly if diabetes was also present.

There is an increasing focus on patients with CKD because its presence in patients who require myocardial revascularisation is growing (14). Data on the comparison between PCI with DES and CABG in this patient group are limited to observational studies (15,16). In a propensity-matched analysis of 893 pairs of patients with a GFR <60 ml/min/1.73 m^2, Chan and co-authors reported that three-year MACCE and survival were significantly lower after CABG than PCI with DES (15). In contrast, in a larger propensity-matched analysis of 2,960 pairs, Bangalore and co-authors found CABG to be associated with short-term death, stroke and repeat revascularisation with only a benefit over PCI with DES regarding four-year rates of MI and repeat revascularisation but not death (16). However, in these retrospective analyses, adjustment for selection bias is not always possible, and many confounding factors may influence the outcomes. Therefore, the results of the current randomised comparison add crucial information to the available body of evidence.

We found that the impact of kidney function on the long-term outcomes of PCI and CABG was significant. Patients with a decreased eGFR between 60 and 90 mL/min/1.73 m^2 had similar rates of hard clinical endpoints of death/stroke/MI when compared to patients with normal kidney function after both CABG and PCI, irrespective of SYNTAX score group, but with a significantly increased risk of repeat revascularisation after PCI. However, patients with CKD had substantially higher rates of the composite of death/stroke/ MI and particularly all-cause death than patients with normal or impaired kidney function. This calls for more dedicated attempts to improve outcomes in this select group. In this regard, CABG was performed more often off-pump to prevent cardiopulmonary bypass circuit-induced adverse effects on renal function. Despite strong evidence supporting

its efficacy after CABG or PCI, the prescription of guideline-directed secondary prevention in patients with CKD was less than in other patients. A lack of evidence, the possibility of dosing errors, a higher incidence of major bleeding, and no clear guideline recommendations for patients with CKD lead to uncertainty among clinicians about the optimal post-treatment medication strategy. Nevertheless, recent publications show that statins significantly reduce cardiovascular events and might be associated with a slower progression of kidney damage (17). Also, benefits of low-dose aspirin on long-term survival without an excess of major bleeding were also noted in patients with CKD (18).

Kidney function was also found to have a significant impact on differences between PCI and CABG outcomes. Patients with a normal kidney function had similar adverse event rates with PCI vs. CABG except for repeat revascularisation that was higher with PCI. In patients with an impaired kidney function, CABG also failed to show a benefit regarding the composite of death/stroke/MI or all-cause death. However, in patients with CKD, there was a clear benefit of CABG over PCI. The difference in MACCE was driven by higher rates of repeat revascularisation, but also due to markedly higher rates of the composite of death/stroke/MI (absolute difference 6.4%) driven by all-cause death (absolute difference 5.5%). This improved survival might be related to the fact that patients with CKD have a higher risk of thrombotic events with PCI as a result of different complex haemostatic properties, severe atherosclerosis, and a lack of antiplatelet treatments.

Interestingly, several subgroups of patients with CKD were at particularly increased risk of adverse events after PCI. While the significant interaction for SYNTAX score and gender is consistent with the overall results of the SYNTAX trial, we found a positive interaction between diabetes and mortality risk of PCI relative to CABG that was not found in the overall SYNTAX trial result[11]. The survival advantage of CABG in this context might be due to the high baseline complexity of coronary dis ease and aggressive nature of the atherosclerotic disease in diabetic patients. In a subgroup analysis of the FREEDOM trial (8), patients with an eGFR of 30-59 mL/min/1.73 m^2 versus those with an eGFR ≥60 mL/min/1.73 m^2 also had significantly higher rates of MACCE and particularly death, similar to the current analy sis. However, the relative difference between PCI and CABG was consistent in patients with and without CKD, suggesting that the combination of CKD and diabetes does not increase the benefit of CABG over PCI, in contrast to the current analysis. Unfortunately, the FREEDOM trial could not distinguish between diabetic and non-diabetic patients with CKD as the study

included only diabetic patients.

Limitations

Some limitations of the current analysis need to be acknowledged. Analyses according to CKD were not predefined in the trial protocol, and the use of TAXUS stents in clinical practice was superseded by second-generation DES, which have been shown to improve long-term outcomes significantly. Therefore, results should be interpreted as observational and hypothesisgenerating. Second, of the CKD patients who were analysed, only 10% had severe and end-stage CKD. Thus, our findings should be restricted to the patients with stage 3 CKD (eGFR 30-60 mL/min/1.73 m^2) before index revascularisation. Third, despite the primarily used CKD-EPI and KDIGO guidelines to define CKD populations that require "the presence of kidney damage at least over three months", estimations of eGFR were only based on the creatinine level at hospital admission. Due to a lack of laboratory data during the periprocedural time, we were unable to determine contrast-induced nephropathy (CIN) and its impact on early and long-term outcomes.

CONCLUSIONS

Patients with CKD have an increased risk of adverse events, particularly mortality, after both PCI and CABG. Differences in five-year event rates between PCI and CABG are shown to have a significant interaction according to kidney function. The negative impact of CKD on long-term outcome following PCI appears to be stronger when compared to CABG, especially in the CKD patients with diabetes and extensive coronary disease. Patients with a normal or impaired kidney function may be candidates for PCI based on a similar risk for adverse events between PCI and CABG except for more repeat revascularisation. These results should provide a more substantiated evidence basis for clinical guideline recommendations for patients with CKD. Nevertheless, an adequately powered, dedicated, randomised trial is needed to provide the evidence for an optimal treatment strategy for patients with CKD who require myocardial revascularisation.

IMPACT ON DAILY PRACTICE

The present study demonstrates a profound negative impact of baseline moderate kidney failure on five-year survival following both PCI and CABG. Importantly, patients are suboptimally treated, although the benefit of a more intense antithrombotic and lipid-lowering postoperative therapy on the outcome is established after surgical and interventional procedures. For treatment decision making, the Heart Team should take into consideration kidney failure, particularly in the presence of diabetes together with higher anatomic complexity as measured by the SYNTAX score.

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Baseline characteristics and 5-year outcomes between the patients with and without baseline glomerular filtration rate estimates.

	PCI cohort			CABG cohort		
	eGFR (n=852)	No eGFR (n=51)	*p*-value	eGFR (n=786)	No eGFR (n=101)	*p*-value
Age, years	65.3±9.7	64.8±9.5	0.73	64.9±9.8	65.1±9.5	0.85
Male	654 (76.8)	36 (70.6)	0.31	627 (79.8)	81 (73.0)	0.10
BMI	28.2±4.8	27.3±4.9	0.23	27.9±4.5	28.0±4.7	0.87
Current smoker	157 (18.8)	10 (20.0)	0.83	177 (23.1)	19 (17.9)	0.23
Medically treated diabetes	219 (25.7)	12 (23.5)	0.73	189 (24.0)	32 (28.8)	0.27
Insulin treatment	86 (10.1)	3 (5.9)	0.33	83 (10.6)	10 (9.0)	0.62
Peripheral vascular disease	78 (9.2)	4 (7.8)	0.75	84 (10.7)	11 (9.9)	0.80
COPD	67 (7.9)	4 (7.8)	>0.99	70 (8.9)	13 (11.7)	0.34
Hypertension	622 (73.5)	41 (82.0)	0.18	591 (75.7)	95 (86.4)	0.053
Hyperlipidaemia	662 (78.3)	43 (86.0)	0.19	606 (77.9)	80 (72.1)	0.17
Carotid artery disease	67 (7.9)	6 (11.8)	0.32	64 (8.1)	11 (9.9)	0.53
History of CVA or TIA	67 (7.9)	2 (4.0)	0.32	73 (9.4)	8 (7.3)	0.49
Unstable angina	253 (29.7)	9 (17.6)	0.067	227 (28.9)	24 (21.6)	0.11
Previous MI	272 (32.3)	13 (25.5)	0.31	264 (34.0)	36 (32.7)	0.79
Congestive heart failure	34 (4.0)	2 (3.9)	0.97	40 (5.2)	7 (6.4)	0.61
Pulmonary hypertension	8 (0.9)	0	0.49	12 (1.5)	0	0.19
LVEF poor (<30%)	10 (1.2)	2 (3.9)	0.096	19 (2.4)	3 (2.7)	0.86
LVEF moderate (30-49%)	148 (17.4)	12 (23.5)	0.26	134 (17.0)	19 (17.1)	0.99
Logistic EuroSCORE	3.8±4.6	3.4±3.5	0.43	3.8±4.1	4.2±6.2	0.48
Left main, any	337 (39.6)	20 (39.2)	0.96	310 (39.5)	38 (34.2)	0.29
Number of lesions	3.9±1.7	3.9±1.5	0.99	4.0±1.7	4.1±1.9	0.52
Bifurcations, any	612 (72.3)	37 (72.5)	0.97	568 (72.8)	83 (75.5)	0.56
Trifurcations, any	94 (11.1)	2 (3.9)	0.11	86 (11.0)	8 (7.3)	0.23
Total occlusion, any	204 (24.1)	13 (25.5)	0.82	176 (22.6)	22 (20.0)	0.54
SYNTAX score	28.4±11.5	28.3±11.4	0.98	29.3±11.4	27.6±11.0	0.13
5-year outcomes						
MACCE	313 (37.5)	19 (41.0)	0.70	200 (27.5)	29 (31.8)	0.41
Death/stroke/MI	173 (20.6)	12 (25.8)	0.45	125 (17.5)	18 (19.4)	0.55
Death, all-cause	113 (13.5)	10 (21.5)	0.13	82 (11.9)	15 (16.5)	0.14
Stroke	19 (2.4)	1 (2.4)	0.98	29 (3.9)	2 (2.1)	0.42
MI	79 (9.7)	4 (9.3)	0.84	29 (3.8)	4 (4.2)	0.88
Repeat revascularisation	213 (26.8)	9 (24.5)	0.46	99 (13.8)	11 (13.5)	0.76

Values are presented as mean±SD or n/N (%). Kaplan-Meier event rates were estimated at 5 years with p-values from log-rank test. BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Supplementary Table 2. Baseline characteristics, 30-day outcomes, and discharge therapy comparison between PCI and CABG groups of patients defined by kidney function.

	Normal kidney function			Impaired kidney function			CKD		
	PCI (n=219)	CABG (n=209)	*p*-value	PCI (n=475)	CABG (n=426)	*p*-value	PCI (n=158)	CABG (n=151)	*p*-value
Age, years	58.8±9.4	59.3±9.9	0.60	66.0±8.7	65.3±8.8	0.25	71.9±7.3	71.6±7.9	0.68
Male	174 (79.5)	173 (82.8)	0.38	372 (78.3)	353 (82.9)	0.086	108 (68.4)	101 (66.9)	0.78
BMI	28.9±5.2	27.5±9.4	0.003	27.8±4.4	28.1±4.5	0.36	28.3±5.3	28.1±4.6	0.70
Current smoker	73 (33.3)	82 (40.2)	0.14	69 (14.5)	77 (18.5)	0.15	15 (9.7)	18 (12.2)	0.49
Medically treated diabetes	46 (21.0)	51 (24.4)	0.40	129 (27.2)	88 (20.7)	0.023	44 (27.8)	50 (33.1)	0.31
Insulin treatment	18 (8.2)	21 (10.0)	0.51	45 (9.5)	39 (9.2)	0.87	23 (14.6)	23 (15.2)	0.87
Peripheral vascular disease	19 (8.7)	13 (6.2)	0.33	38 (8.0)	47 (11.0)	0.12	21 (13.3)	24 (15.9)	0.52
COPD	19 (8.7)	22 (10.5)	0.52	33 (6.9)	33 (7.7)	0.65	15 (9.5)	15 (9.9)	0.90
Hypertension	144 (66.1)	155 (74.9)	0.046	343 (72.8)	308 (72.6)	0.95	135 (86.0)	128 (85.3)	0.87
Hyperlipidaemia	164 (75.2)	166 (79.8)	0.26	376 (79.8)	321 (76.4)	0.22	122 (77.7)	119 (79.3)	0.73
Carotid artery disease	9 (4.1)	10 (4.8)	0.73	39 (8.2)	29 (6.8)	0.43	19 (12.0)	25 (16.6)	0.25
History of CVA or TIA	9 (4.1)	15 (7.2)	0.16	36 (7.6)	39 (9.2)	0.37	22 (14.0)	19 (12.7)	0.73
Unstable angina	69 (31.5)	58 (27.8)	0.39	142 (29.9)	125 (29.3)	0.86	42 (26.6)	44 (29.1)	0.62
Previous MI	74 (34.1)	84 (40.2)	0.19	140 (29.9)	133 (31.6)	0.59	58 (36.9)	47 (32.0)	0.36
Congestive heart failure	3 (1.4)	8 (3.9)	0.10	16 (3.4)	17 (4.1)	0.60	15 (9.6)	15 (10.3)	0.83
Pulmonary hypertension	3 (1.4)	1 (0.5)	0.34	3 (0.6)	4 (0.9)	0.60	2 (1.3)	7 (4.6)	0.078
LVEF poor (<30%)	2 (0.9)	3 (1.4)	0.61	5 (1.1)	8 (1.9)	0.30	3 (1.9)	8 (5.3)	0.11
LVEF moderate (30-49%)	36 (16.4)	41 (19.6)	0.39	74 (15.6)	68 (16.0)	0.87	38 (24.1)	25 (16.6)	0.10
Logistic EuroSCORE	2.7±3.1	2.8±2.9	0.67	3.6±4.7	3.4±3.3	0.58	6.0±5.3	6.3±6.1	0.58
Left main, any	94 (42.9)	87 (41.6)	0.79	176 (37.1)	163 (38.4)	0.69	67 (42.4)	60 (39.7)	0.63
Number of lesions	3.9±1.9	4.0±1.7	0.61	3.9±1.6	3.9±1.6	0.94	4.0±1.6	4.1±1.9	0.61
Bifurcations, any	154 (70.6)	148 (71.5)	0.53	341 (72.2)	313 (73.8)	0.60	117 (75.0)	107 (71.8)	0.53
Trifurcations, any	18 (8.3)	31 (15.0)	0.036	57 (12.1)	47 (11.1)	0.64	19 (12.2)	8 (5.4)	0.036
Total occlusion, any	47 (21.6)	40 (19.3)	0.91	116 (24.6)	96 (22.6)	0.50	41 (26.3)	40 (26.8)	0.91
SYNTAX score	27.4±11.2	28.8±11.7	0.20	28.5±11.3	29.5±11.2	0.17	29.6±12.3	29.3±11.7	0.86
Complete revascularisation	122 (56.5)	124 (61.4)	0.31	282 (60.5)	279 (66.4)	0.068	73 (46.2)	91 (60.7)	0.011
30-day post-treatment outcomes									
MACCE	14 (6.4)	12 (5.8)	0.77	24 (5.1)	18 (4.2)	0.56	10 (6.3)	6 (4.0)	0.34
Death/stroke/MI	11 (5.0)	10 (4.8)	0.91	20 (4.2)	17 (4.0)	0.87	9 (5.7)	4 (2.6)	0.18
Death, all-cause	4 (1.8)	2 (1.0)	0.45	8 (1.7)	2 (0.5)	0.083	4 (2.5)	1 (0.7)	0.19
Repeat revascularisation	8 (3.7)	4 (1.9)	0.28	15 (3.2)	5 (1.2)	0.054	3 (1.9)	2 (1.3)	0.68
Medication at discharge									
Acetylsalicylic acid	216 (99.1)	189 (91.7)	0.008	456 (96.4)	378 (89.2)	<0.001	147 (93.0)	125 (83.3)	0.008
Thienopyridine antiplatelet	214 (98.2)	42 (20.4)	<0.001	458 (96.8)	70 (16.5)	<0.001	149 (94.3)	27 (18.0)	<0.001
ARB or ACE inhibitor	140 (64.2)	102 (49.5)	<0.001	324 (68.5)	215 (50.7)	<0.001	109 (69.0)	73 (48.7)	<0.001
β-blocker	176 (80.7)	160 (77.7)	0.55	388 (82.0)	333 (78.5)	0.19	122 (72.2)	120 (80.0)	0.55

Supplementary Table 2. Continued.

Calcium channel blockers	36 (16.5)	41 (19.9)	<0.001	132 (27.9)	72 (17.0)	<0.001	53 (33.5)	24 (16.0)	<0.001
Amiodarone	5 (2.3)	23 (11.2)	<0.001	3 (0.6)	59 (13.9)	<0.001	4 (2.5)	22 (14.7)	<0.001
Statins	188 (86.2)	152 (73.8)	0.099	418 (88.4)	322 (75.9)	<0.001	132 (83.5)	114 (76.0)	0.099

Values are presented as mean±SD or n/N (%). Kaplan-Meier event rates were estimated at 30 days with p-values from log-rank test. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Supplementary Table 3. Baseline characteristics of patients by kidney function within PCI and CABG randomised cohorts.

	PCI cohort				CABG cohort			
	Normal kidney function (n=219)	impaired kidney function (n=475)	CKD (n=158)	*p*-value	Normal kidney function (n=209)	impaired kidney function (n=426)	CKD (n=151)	*p*-value
Age, years	58.8±9.4	66.0±8.7	71.9±7.3	<0.001	59.3±9.9	65.3±8.8	71.6±7.9	<0.001
Male	174 (79.5)	372 (78.3)	108 (68.4)	0.020	173 (82.8)	353 (82.9)	101 (66.9)	<0.001
BMI	28.9±5.2	27.8±4.4	28.3±5.3	0.022	27.5±9.4	28.1±4.5	28.1±4.6	0.24
Current smoker	73 (33.3)	69 (14.5)	15 (9.7)	<0.001	82 (40.2)	77 (18.5)	18 (12.2)	<0.001
Medically treated diabetes	46 (21.0)	129 (27.2)	44 (27.8)	0.18	51 (24.4)	88 (20.7)	50 (33.1)	0.009
Insulin treatment	18 (8.2)	45 (9.5)	23 (14.6)	0.10	21 (10.0)	39 (9.2)	23 (15.2)	0.11
Peripheral vascular disease	19 (8.7)	38 (8.0)	21 (13.3)	0.13	13 (6.2)	47 (11.0)	24 (15.9)	0.013
COPD	19 (8.7)	33 (6.9)	15 (9.5)	0.51	22 (10.5)	33 (7.7)	15 (9.9)	0.45
Hypertension	144 (66.1)	343 (72.8)	135 (86.0)	<0.001	155 (74.9)	308 (72.6)	128 (85.3)	0.007
Hyperlipidaemia	164 (75.2)	376 (79.8)	122 (77.7)	0.39	166 (79.8)	321 (76.4)	119 (79.3)	0.56
Carotid artery disease	9 (4.1)	39 (8.2)	19 (12.0)	0.017	10 (4.8)	29 (6.8)	25 (16.6)	<0.001
History of CVA or TIA	9 (4.1)	36 (7.6)	22 (14.0)	0.002	15 (7.2)	39 (9.2)	19 (12.7)	0.22
Unstable angina	69 (31.5)	142 (29.9)	42 (26.6)	0.58	58 (27.8)	125 (29.3)	44 (29.1)	0.91
Previous MI	74 (34.1)	140 (29.9)	58 (36.9)	0.21	84 (40.2)	133 (31.6)	47 (32.0)	0.085
Congestive heart failure	3 (1.4)	16 (3.4)	15 (9.6)	<0.001	8 (3.9)	17 (4.1)	15 (10.3)	0.009
Pulmonary hypertension	3 (1.4)	3 (0.6)	2 (1.3)	0.58	1 (0.5)	4 (0.9)	7 (4.6)	0.002
LVEF poor (<30%)	2 (0.9)	5 (1.1)	3 (1.9)	0.64	3 (1.4)	8 (1.9)	8 (5.3)	0.035
LVEF moderate (30-49%)	36 (16.4)	74 (15.6)	38 (24.1)	0.047	41 (19.6)	68 (16.0)	25 (16.6)	0.51
Logistic EuroSCORE	2.7±3.1	3.6±4.7	6.0±5.3	<0.001	2.8±2.9	3.4±3.3	6.3±6.1	<0.001
Left main, any	94 (42.9)	176 (37.1)	67 (42.4)	0.24	87 (41.6)	163 (38.4)	60 (39.7)	0.73
Number of lesions	3.9±1.9	3.9±1.6	4.0±1.6	0.89	4.0±1.7	3.9±1.6	4.1±1.9	0.86
Bifurcations, any	154 (70.6)	341 (72.2)	117 (75.0)	0.65	148 (71.5)	313 (73.8)	107 (71.8)	0.79
Total occlusion, any	47 (21.6)	116 (24.6)	41 (26.3)	0.54	40 (19.3)	96 (22.6)	40 (26.8)	0.25
SYNTAX score	27.4±11.2	28.5±11.3	29.6±12.3	0.18	28.8±11.7	29.5±11.2	29.3±11.7	0.79

BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Supplementary Table 4. Procedural characteristics, 30-day outcomes and discharge therapies of patients by kidney function within PCI and CABG randomised cohorts.

	PCI cohort				CABG cohort			
	Normal kidney function (n=219)	Impaired kidney function (n=475)	CKD (n=158)	*p*-value	Normal kidney function (n=209)	Impaired kidney function (n=426)	CKD (n=151)	*p*-value
Procedural characteristics								
Bypass time (min)	-	-	-	-	86.1±31.3	85.4±36.0	86.4±36.9	0.83
Cross-clamp time (min)	-	-	-	-	54.9±23.3	54.0±25.3	54.9±23.0	0.77
Off-pump surgery	-	-	-	-	32 (15.8)	55 (13.1)	33 (22.1)	0.035
LIMA use	-	-	-	-	197 (97.5)	410 (97.6)	142 (94.7)	0.17
BIMA use	-	-	-	-	68 (34.2)	119 (28.5)	28 (18.8)	0.007
Complete arterial	-	-	-	-	45 (22.3)	77 (18.3)	22 (14.7)	0.19
No. of distal anastomoses, n	-	-	-	-	3.2±0.9	3.3±0.9	3.2±0.9	0.55
No. of stents implanted, n	4.7±2.5	4.7±2.2	4.5±2.1	0.64	-	-	-	-
Total stents implanted (mm)	88.1±54.2	87.1±46.3	82.4±44.1	0.58	-	-	-	-
Long stenting (>100 mm)	78 (36.3)	155 (33.5)	47 (29.7)	0.51	-	-	-	-
Overlapping stents, any	119 (55.1)	241 (51.7)	86 (54.8)	0.64	-	-	-	-
Staged procedure	38 (17.4)	57 (12.0)	23 (14.6)	0.16	-	-	-	-
Complete revascularisation	122 (56.5)	282 (60.5)	73 (46.2)	0.007	124 (61.4)	279 (66.4)	91 (60.7)	0.30
Medication at discharge								
Acetylsalicylic acid	216 (99.1)	456 (96.4)	147 (93.0)	0.006	189 (91.7)	378 (89.2)	125 (83.0)	0.043
Thienopyridine antiplatelet	214 (98.2)	458 (96.8)	149 (94.3)	0.11	42 (20.4)	70 (16.5)	27 (18.0)	0.49
ARB or ACE inhibitor	140 (64.2)	324 (68.5)	109 (69.0)	0.49	102 (49.5)	215 (50.7)	73 (48.7)	0.90
β-blocker	176 (80.7)	388 (82.0)	122 (77.2)	0.41	160 (77.7)	333 (78.5)	120 (80.0)	0.87
Calcium channel blockers	36 (16.5)	132 (27.9)	53 (33.5)	<0.001	41 (19.9)	72 (17.0)	24 (16.0)	0.57
Amiodarone	5 (2.3)	3 (0.6)	4 (2.5)	0.096	23 (11.2)	59 (13.9)	22 (14.7)	0.55
Statins	188 (86.2)	418 (88.4)	132 (83.5)	0.28	152 (73.8)	322 (75.9)	114 (76.0)	0.82
30-day post-treatment outcomes								
MACCE	14 (6.4)	24 (5.1)	10 (6.3)	0.70	12 (5.8)	18 (4.2)	6 (4.0)	0.63
Death/stroke/MI	11 (5.0)	20 (4.2)	9 (5.7)	0.71	10 (4.8)	17 (4.0)	4 (2.6)	0.58
Death, all-cause	4 (1.8)	8 (1.7)	4 (2.5)	0.78	2 (1.0)	2 (0.5)	1 (0.7)	0.76
Repeat revascularisation	8 (3.7)	15 (3.2)	3 (1.9)	0.62	4 (1.9)	5 (1.2)	2 (1.3)	0.75

Values are presented as mean±SD or n/N (%). Kaplan-Meier event rates were estimated at 30 days with p-values from log-rank test.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BIMA, bilateral internal mammary artery; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; LIMA, left internal mammary artery; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention Values are present as mean±SD or n/N (%). Kaplan–Meier event rates were estimated at 30-day with p-values from log-rank test.

Supplementary Table 5. Outcomes at 5 years stratified by baseline kidney function in the PCI and CABG cohorts.

	PCI cohort					CABG cohort				
	Normal kidney function	Impaired kidney function	CKD	*p*-value normal vs. impaired	*p*-value normal vs. CKD	Normal kidney function	Impaired kidney function	CKD	*p*-value normal vs. impaired	*p*-value normal vs. CKD
MACCE	73 (34.9)	174 (37.3)	66 (42.1)	0.42	0.075	56 (29.6)	102 (25.1)	42 (31.5)	0.43	0.75
Death/stroke/MI	40 (18.4)	83 (17.7)	50 (31.9)	0.80	0.002	30 (16.5)	62 (15.3)	33 (25.5)	0.98	0.051
Death, all-cause	21 (10.8)	51 (10.9)	41 (26.7)	0.63	<0.001	18 (10.6)	37 (9.3)	27 (21.2)	0.97	0.005
Cardiac death	15 (6.9)	30 (6.6)	27 (17.9)	0.82	0.001	11 (5.7)	13 (3.2)	10 (7.4)	0.17	0.34
Vascular death	1 (0.5)	4 (0.9)	1 (0.7)	0.57	0.77	1 (0.5)	2 (0.5)	1 (0.8)	0.97	0.78
Non-cardiovascular death	5 (2.5)	17 (3.8)	13 (9.4)	0.36	0.003	6 (2.7)	20 (5.3)	15 (12.0)	0.31	0.003
Stroke	5 (2.4)	8 (1.8)	6 (4.3)	0.61	0.31	7 (3.6)	18 (4.4)	4 (3.0)	0.61	0.77
MI	24 (11.1)	39 (8.6)	16 (11.1)	0.26	0.96	10 (4.9)	13 (3.1)	6 (4.2)	0.26	0.73
Repeat revascularisation	57 (28.2)	125 (27.7)	31 (21.9)	0.86	0.32	34 (17.6)	53 (13.4)	12 (8.9)	0.18	0.039

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplementary Table 6. Outcomes at 5 years stratified by baseline kidney function.

	PCI	CABG	HR (95% CI)	*p*-value
Normal kidney function, n	219	209		
MACCE	73 (34.9)	56 (29.6)	1.25 (0.88-1.77)	0.21
Death/stroke/MI	40 (18.4)	30 (16.5)	1.24 (0.77-1.99)	0.37
Death, all-cause	21 (10.8)	18 (10.6)	1.06 (0.57-2.00)	0.85
Cardiac death	15 (6.9)	11 (5.7)	1.24 (0.57-2.71)	0.58
Vascular death	1 (0.5)	1 (0.5)	0.92 (0.12-14.65)	0.95
Non-cardiovascular death	5 (2.5)	6 (2.7)	0.75 (0.23-2.47)	0.64
Stroke	5 (2.4)	7 (3.6)	0.65 (0.21-2.06)	0.46
MI	24 (11.1)	10 (4.9)	2.25 (1.08-4.72)	0.026
Repeat revascularisation	57 (28.2)	34 (17.6)	1.63 (1.06-2.49)	0.023
Impaired kidney function, n	475	426		
MACCE	174 (37.3)	102 (25.1)	1.60 (1.25-2.04)	<0.001
Death/stroke/MI	83 (17.7)	62 (15.3)	1.18 (0.85-1.63)	0.33
Death, all-cause	51 (10.9)	37 (9.3)	1.22 (0.80-1.86)	0.36
Cardiac death	30 (6.6)	13 (3.2)	2.04 (1.08-3.92)	0.028
Vascular death	4 (0.9)	2 (0.5)	1.76 (0.32-9.64)	0.51
Non-cardiovascular death	17 (3.8)	20 (5.3)	0.75 (0.39-1.43)	0.38
Stroke	8 (1.8)	18 (4.4)	0.39 (0.17-0.89)	0.021
MI	39 (8.6)	13 (3.1)	2.70 (1.44-5.06)	0.001
Repeat revascularisation	125 (27.7)	53 (13.4)	2.25 (1.63-3.10)	<0.001
CKD, n	158	151		
MACCE	66 (42.1)	42 (31.5)	1.58 (1.08-2.33)	0.019
Death/stroke/MI	50 (31.9)	33 (25.5)	1.45 (0.93-2.25)	0.096
Death, all-cause	41 (26.7)	27 (21.2)	1.44 (0.88-2.34)	0.14
Cardiac death	27 (17.9)	10 (7.4)	2.33 (1.26-4.70)	0.011
Vascular death	1 (0.7)	1 (0.8)	0.92 (0.16-14.71)	0.95
Non-cardiovascular death	13 (9.4)	15 (12.0)	0.82 (0.39-1.72)	0.59
Stroke	6 (4.3)	4 (3.0)	1.40 (0.39-4.95)	0.60
MI	16 (11.1)	6 (4.2)	2.55 (1.03-6.52)	0.042
Repeat revascularisation	31 (21.9)	12 (8.9)	2.56 (1.31-4.99)	0.004

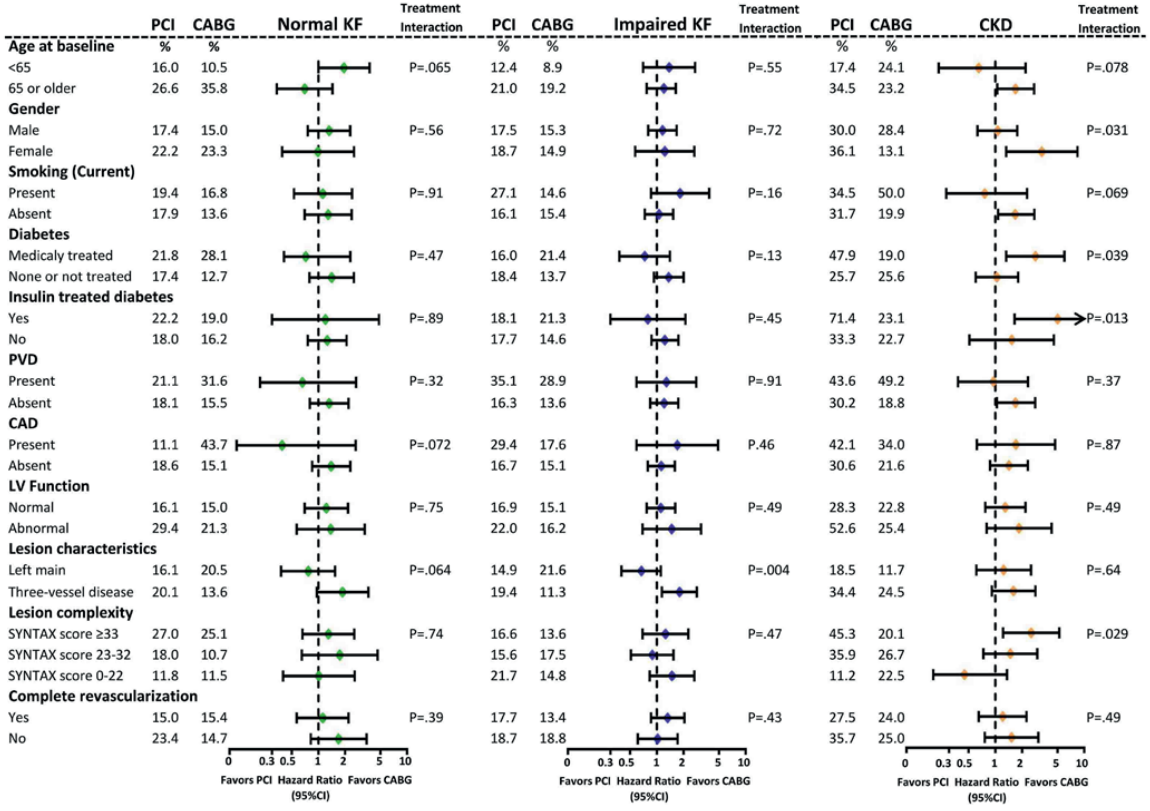
Values are presented as n/N (%). Data are Kaplan-Meier estimates of adverse events. p-values are from log-rank test. Treatment-by-kidney status interactions failed to reach statistical significance for MACCE (p_{int}=0.15), the composite safety endpoint (p_{int}=0.070), all-cause death (p_{int}=0.017), cardiac death (p_{int}=0.009), vascular death (p_{int}=0.89), stroke (p_{int}=0.21), MI (p_{int}=0.96) and repeat revascularisation (p_{int}=0.65). CABG: coronary artery bypass grafting; CKD, chronic kidney disease; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplementary Table 7. Five-year clinical outcomes according to kidney function and diabetes status.

	Non-diabetic (n=1,230)			Diabetic (n=398)			
	PCI	CABG	p-value	PCI	CABG	p-value	Interaction p-value*
Normal kidney function, n	173	158		56	41		
MACCE	54 (31.3)	39 (26.0)	0.26	19 (46.8)	17 (40.6)	0.47	0.97
Death/stroke/MI	30 (17.4)	19 (12.7)	0.24	10 (21.8)	11 (28.1)	0.95	0.47
Death, all-cause	14 (8.2)	11 (7.6)	0.80	7 (15.2)	7 (21.1)	0.92	0.95
Repeat revascularisation	43 (25.3)	26 (17.6)	0.085	14 (38.4)	8 (17.7)	0.11	0.55
Impaired kidney function, n	346	338		129	88		
MACCE	115 (33.7)	76 (23.3)	0.004	59 (47.0)	26 (32.3)	0.031	0.64
Death/stroke/MI	63 (18.4)	45 (13.7)	0.11	20 (16.0)	17 (21.4)	0.35	0.13
Death, all-cause	34 (9.9)	25 (7.8)	0.30	17 (13.7)	12 (15.6)	0.84	0.48
Repeat revascularisation	75 (22.8)	39 (12.3)	<0.001	50 (40.9)	14 (17.7)	0.001	0.25
CKD, n	114	101		44	50		
MACCE	43 (38.1)	30 (32.6)	0.31	23 (52.4)	12 (28.6)	0.005	0.10
Death/stroke/MI	29 (25.7)	23 (25.6)	0.89	21 (47.9)	10 (24.4)	0.005	0.039
Death, all-cause	23 (20.5)	20 (22.5)	0.83	18 (40.9)	7 (17.7)	0.004	0.018
Repeat revascularisation	21 (20.2)	9 (10.4)	0.070	10 (26.6)	3 (7.1)	0.015	0.39

*Interaction term for diabetes status by treatment arm.

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.



Supplementary Figure 1. Hazard ratios of PCI versus CABG according to subgroups based on patient characteristics by the status of kidney function. Values are Kaplan-Meier event rates at 5 years. CABG, coronary artery bypass grafting; CAD, carotid artery disease; HR, hazard ratio; KF, kidney function; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Chapter 13

Bypass Surgery or Stenting for Left Main Coronary Artery Disease in Patients with Diabetes

Milojevic M, Serruys PW, Sabik JF, Kandzari DE, Schampaert E, van Boven AJ, Horkay F, Ungi I, Mansour S, Banning A, Taggart DP, Sabaté M, Gershlick A, Bochenek A, Pomar J, Lembo N, Noiseux N, Puskas JD, Crowley A, Kosmidou I, Mehran R, Ben-Yehuda O, Généreux P, Pocock SJ, Simonton CA, Stone GW, Kappetein AP.

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ABSTRACT

BACKGROUND: The randomized EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial reported a similar rate of the 3-year composite primary endpoint of death, myocardial infarction (MI), or stroke in patients with left main coronary artery disease (LMCAD) and site-assessed low or intermediate SYNTAX scores treated with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Whether these results are consistent in high-risk patients with diabetes, who have fared relatively better with CABG in most prior trials, is unknown.

OBJECTIVES: In this pre-specified subgroup analysis from the EXCEL trial, the authors sought to examine the effect of diabetes in patients with LMCAD treated with PCI versus CABG.

METHODS: Patients (N = 1,905) with LMCAD and site-assessed low or intermediate CAD complexity (SYNTAX scores <=32) were randomized 1:1 to PCI with everolimus-eluting stents versus CABG, stratified by the presence of diabetes. The primary endpoint was the rate of a composite of all-cause death, stroke, or MI at 3 years. Outcomes were examined in patients with (n = 554) and without (n = 1,350) diabetes.

RESULTS: The 3-year composite primary endpoint was significantly higher in diabetic compared with nondiabetic patients (20.0% vs. 12.9%; p < 0.001). The rate of the 3-year primary endpoint was similar after treatment with PCI and CABG in diabetic patients (20.7% vs. 19.3%, respectively; hazard ratio: 1.03; 95% confidence interval: 0.71 to 1.50; p = 0.87) and nondiabetic patients (12.9% vs. 12.9%, respectively; hazard ratio: 0.98; 95% confidence interval: 0.73 to 1.32; p = 0.89). All-cause death at 3 years occurred in 13.6% of PCI and 9.0% of CABG patients (p = 0.046), although no significant interaction was present between diabetes status and treatment for all-cause death (p = 0.22) or other endpoints, including the 3-year primary endpoint (p = 0.82) or the major secondary endpoints of death, MI, or stroke at 30 days (p = 0.61) or death, MI, stroke, or ischemia-driven revascularization at 3 years (p = 0.65).

CONCLUSIONS: In the EXCEL trial, the relative 30-day and 3-year outcomes of PCI with everolimus-eluting stents versus CABG were consistent in diabetic and nondiabetic patients with LMCAD and site-assessed low or intermediate SYNTAX scores.

INTRODUCTION

The number of people with diabetes mellitus is increasing, having risen from 108 million in 1980 to 422 million in 2014 (1). Patients with diabetes are at an increased risk for systemic atherosclerosis and advanced coronary artery disease (CAD), and diabetes is a predictor of adverse events after both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) (2,3). In patients with diabetes and complex anatomic disease, CABG has been associated with lower mortality rates compared with PCI (3–5). As a result, CABG has been recommended as the standard of care for patients with diabetes and complex CAD including left main coronary artery disease (LMCAD) (6); however, in a recent pooled analysis of 3 randomized trials (2 of which were performed more than a decade ago), patients with diabetes and low or intermediate anatomic complexity as signified by a SYNTAX score of <=32 had similar 5-year rates after PCI and CABG of all-cause death, cardiac death, and the composite of death, myocardial infarction (MI), or stroke (7).

Conversely, patients with high (>=33) SYNTAX scores had significantly higher adverse event rates with PCI compared with CABG. Since the performance of these trials, both PCI technology and technique, as well as surgical methods and outcomes, have continued to improve. The extent to which diabetes thus influences outcomes after contemporary revascularization strategies in patients with LMCAD is unknown.

The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was a large-scale study in which selected patients with LMCAD were randomized to PCI with everolimus-eluting stents (EES) versus CABG (8). Acknowledging the importance of diabetes, randomization was stratified by the presence of this variable to ensure a balanced baseline in the diabetic and nondiabetic strata. The present report describes the prespecified subgroup analysis examining the impact of diabetes on 30-day and 3-year outcomes after PCI versus CABG in patients with LMCAD.

METHODS

STUDY DESIGN. The protocol, patient eligibility criteria, and methods of the EXCEL trial have been reported previously (9). The EXCEL trial was a prospective, multinational, unblinded randomized trial in which 1,905 patients with de novo

LMCAD and siteassessed SYNTAX scores <=32 in whom equipoise was present for transcatheter versus surgical revascularization were randomly (1:1) assigned to undergo PCI with cobalt–chromium fluoropolymer-based EES (Abbott Vascular, Santa Clara, California) or CABG. Patients were assessed for eligibility at each participating site by a heart team that consisted of (at least) an interventional cardiologist and a cardiac surgeon (10). Randomization was stratified according to the presence of diabetes and site. The trial was approved by the investigational review board or ethics committee at each participating center. All patients provided written informed consent before enrollment. The trial was funded by Abbott Vascular but led by a broad academic group with equal representation of interventional cardiologists and cardiac surgeons (8,9). The trial is registered at clinicaltrials.gov, identifier NCT01205776.

ENDPOINTS AND DEFINITIONS. The primary endpoint was the 3-year rate of all-cause mortality, stroke, or MI. Major powered secondary outcomes included this endpoint at 30 days and the composite rate of death, stroke, MI, or ischemia-driven revascularization (IDR) at 3 years. Other secondary endpoints included the components of the primary and secondary endpoints as well as revascularization, stent thrombosis, symptomatic graft stenosis or occlusion, and a prespecified composite of periprocedural major adverse events.

The definitions of these outcome measures have been previously described in detail (8,9). In brief, stroke was defined as a focal neurological deficit of central origin lasting >24 h, confirmed by a neurologist and imaging. Post-procedure MI was defined as the rise within 72 h after PCI or CABG of creatine kinase-myocardial band (CK-MB) to >10x the upper reference limit (URL), or >5x URL plus new pathological Q waves in at least 2 contiguous leads or new persistent non–rate-related left bundle branch block, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Spontaneous MI was defined as the occurrence >72 h after PCI or CABG of a rise and fall of cardiac biomarkers (CK-MB or troponin) >1x URL plus electrocardiogram changes indicative of new ischemia, or development of pathological Q waves in >2 contiguous electrocardiogram leads, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Revascularization events were classified as either ischemia-driven or non–ischemia-driven by pre-specified criteria (9). An independent clinical

events committee adjudicated all primary and secondary endpoints with source document verification.

Patients with diabetes at baseline were categorized according to treatment as: 1) insulin-treated (with or without oral hypoglycemic agents); 2) oral hypoglycemic agent–treated without insulin; and 3) nonpharmacological therapy only, including dietary modification, exercise, and weight reduction. Using this classification, the following diabetes subgroups were defined and analyzed in the present study: 1) insulin-treated patients with or without oral hypoglycemic agents; and 2) non–insulin-treated patients (because only a small number of patients were treated without medications).

STATISTICAL ANALYSIS. Subgroup analysis according to diabetes status with formal interaction testing was pre-specified in the trial protocol, although no formal statistical hypothesis was defined a priori. All analyses were performed with data from the time of randomization in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned, regardless of the treatment received. Data are summarized using descriptive statistics, presented as proportions (%, count/sample size) or mean ± SD. Continuous variables were compared using the Student's *t*-test; differences in categorical variables were assessed with the chi-square test or Fisher exact test, as appropriate. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared by the log-rank test. Multivariable predictors of 3-year outcomes were identified using stepwise selection with a significance level of <0.10 for entry and exit in a logistic regression model. p Values for interaction were generated by logistic regression chi-square test. Analyses according to SYNTAX score tertiles (low 0 to 22, intermediate 23 to 32, high >=33) were performed using 3-year Kaplan-Meier event estimates. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. Baseline diabetes status was known in 1,904 of 1,905 randomized patients. Diabetes was present in 554 of 1,904 patients (29.1%); 147 patients were treated with insulin, 358 were treated with oral hypoglycemic agents without insulin, and 49 were treated with nonpharmacological measures. Patients with diabetes had a significantly greater number of comorbidities compared with nondiabetic patients, including hypertension, hyperlipidemia,

anemia, renal insufficiency, peripheral vascular disease, congestive heart failure, prior stroke, and a higher STS score, although were less likely to be current smokers (Table 1). By core laboratory analysis, diabetic patients also had a higher SYNTAX score, more frequently had diffuse or small vessel disease, and had a greater number of treated lesions.

As shown in Table 2, bilateral internal mammary artery (BIMA) grafting was performed significantly less frequently in patients with diabetes compared with patients without diabetes (19.6% vs. 32.4%; $p < 0.001$). Off-pump CABG technique, total bypass time, and the number of grafts did not differ between groups. Mean PCI duration was significantly longer in diabetic than in nondiabetic patients. There were no significant differences between the groups in other PCI procedural aspects. At hospital discharge, no differences in the administration of antiplatelet agents, statins, and beta-blockers were found between diabetic and nondiabetic patients after both PCI and CABG (Table 2). Medication use during follow-up is presented in Supplemental Table 1.

THIRTY-DAY OUTCOMES. As shown in Table 3, the 30-day rates of major adverse events were not significantly different in diabetic compared with nondiabetic patients; however, in both diabetic and nondiabetic patients, the 30-day rate of the composite endpoint of death, stroke, or MI was higher after CABG than after PCI. The difference in outcome was driven mainly by higher rates of stroke and MI after CABG, whereas rates of all-cause death and ischemiadriven revascularization were similar between CABG and PCI. Major adverse events were also higher after CABG than PCI in both diabetic and nondiabetic patients. Acute renal failure within 30 days occurred more commonly in patients with diabetes compared with those without diabetes (2.7% vs. 1.1%; $p = 0.01$), and was more frequent after revascularization with CABG compared with PCI both in patients with (4.1% vs. 1.4%; $p = 0.005$) and without (1.9% vs. 0.3%; $p = 0.05$) diabetes ($p_{interaction} = 0.44$) (Supplemental Table 2). Among CABG patients, sternal wound dehiscence occurred in 0.4% versus 1.2% of diabetic and nondiabetic patients, respectively ($p = 0.26$). Furthermore, sternal dehiscence did not occur more often after the use of BIMA compared with the single internal mammary artery technique (0% vs. 0.5%; $p = 0.68$). There were no significant interactions between diabetes status and treatment for any of the 30-day study endpoints.

Table 1. Baseline Characteristics of Patients According to Diabetes Status in the Overall Cohort.

	No Diabetes (n = 1,350)	Diabetes (n = 554)	*p* Value
Age, yrs	65.7 ± 9.7	66.5 ± 9.2	0.17
Male	78.0 (10,53/1,350)	74.0 (410/554)	0.06
Body mass index, kg/m^2	28.0 ± 4.5	30.4 ± 5.5	<0.001
Hyperlipidemia treated with medication	65.7 (886/1,348)	80.5 (445/553)	<0.001
Hypertension treated with medication	68.2 (921/1,350)	87.5 (485/554)	<0.001
Current smoker	23.9 (321/1,343)	17.3 (95/548)	0.002
Prior myocardial infarction	17.1 (229/1,339)	18.4 (101/549)	0.50
Congestive heart failure	5.7 (77/1,345)	8.9 (49/553)	0.01
History of carotid artery disease	7.3 (98/1,345)	10.5% (58/551)	0.02
Prior stroke	3.0 (41/1,349)	5.1 (28/554)	0.03
Prior transient ischemic attack	2.8 (38/1,343)	3.5 (19/550)	0.47
Peripheral vascular disease	7.7 (103/1,344)	14.1 (78/552)	<0.001
Chronic kidney disease*	14.5 (191/1,320)	21.3 (117/549)	<0.001
Anemia†	20.1 (268/1,334)	36.1 (200/554)	<0.001
Recent myocardial infarction, within 7 days	15.1 (203/1,345)	14.3 (79/552)	0.66
Unstable angina without recent myocardial infarction	23.1 (311/1,345)	27.7 (153/552)	0.03
Prior percutaneous coronary intervention	15.3 (206/1,348)	21.7 (120/554)	<0.001
Left ventricular ejection fraction, %	57.4 ± 9.1	56.6 ± 9.8	0.19
Society of Thoracic Surgeons score	0.85 ± 0.81	0.96 ± 0.91	0.01
SYNTAX score			
Site-assessed	20.5 ± 6.3	20.8 ± 5.9	0.25
0–22	61.8 (833/1,348)	57.1 (316/553)	0.060
23–32	38.2 (515/1,348)	42.9 (237/553)	0.060
>=33	0 (0/1,348)	0 (0/553)	—
Core laboratory assessed	26.2 ± 9.4	27.3 ± 9.1	0.02
0–22	37.7 (491/1,302)	31.1 (167/537)	0.007
23–32	38.6 (502/1,302)	43.6 (234/537)	0.047
>=33	23.7 (309/1,302)	25.3 (136/537)	0.47
Coronary anatomy, core laboratory-assessed Left main	56.3 (568/1,009)	62.6 (253/404)	0.03
distal bifurcation involvement Number of lesions treated per patient	2.2 ± 0.9	2.3 ± 0.9	0.02
Number of treated non-left main diseased vessels	1.5 ± 1.0	1.7 ± 1.0	<0.001
0	18.8 (250/1,328)	14.6 (80/549)	0.03
1	32.8 (435/1,328)	27.1 (149/549)	0.02
2	31.3 (416/1,328)	37.2 (204/549)	0.01
3	17.1 (227/1,328)	21.1 (116/549)	0.04
Diffuse disease or small vessels	4.7 (62/1,321)	9.3 (51/549)	<0.001

Values are mean ± SD or % (n/N). *Estimated glomerular filtration rate <60 ml/min. †Hemoglobin <12 g/dl in women and <13 g/dl in men.

Table 2. Procedural Characteristics and Discharge Medications According to Diabetes Status and Revascularization Assignment.

	CABG (n = 956)			PCI (n = 948)		
	No Diabetes (n = 688)	Diabetes (n = 268)	*p* Value	No Diabetes (n = 662)	Diabetes (n = 286)	*p* Value
Procedural characteristics						
Assigned procedure performed	97.0 (667/688)	95.5 (256/268)	0.28	98.6 (653/662)	98.6 (282/286)	0.96
Time to procedure, days	6.8 ± 15.1	6.5 ± 11.9	0.69	3.4 ± 5.7	3.0 ± 4.1	0.73
Procedure duration, min	241.9±70.9	246.2 ±69.2	0.37	80.2 ± 41.8	87.7 ± 41.8	0.005
Off-pump CABG	30.1 (201/667)	27.3 (70/256)	0.40	—	—	—
Bypass time, min	81.6 ± 42.4	87.4 ± 51.0	0.21	—	—	—
Any internal mammary artery used	99.1 (658/664)	98.0 (250/255)	0.19	—	—	—
Both internal mammary arteries used	32.4 (215/664)	19.6 (50/255)	<0.001	—	—	—
No. of grafts	2.5 ± 0.8	2.6 ± 0.8	0.50	—	—	—
No. of stents implanted	—	—	—	2.4 ± 1.5	2.6 ± 1.5	0.08
Total stent length, mm	—	—	—	48.0 ± 35.4	51.7 ± 36.4	0.09
Distal LMCA bifurcation treated	—	—	—	56.7 (366/645)	58.2 (163/280)	0.68
2-stent approach	—	—	—	33.1 (121/366)	39.3 (64/163)	0.17
Crush or mini-crush	—	—	—	10.3 (12/117)	21.9 (14/64)	0.03
FFR used	—	—	—	9.0 (59/653)	8.9 (25/281)	0.95
IVUS used	—	—	—	77.3 (505/653)	77.0 (217/282)	0.90
Duration of hospital stay, days	12.5 ± 9.5	13.2 ± 9.9	0.66	5.4 ± 5.3	5.5 ± 5.1	0.33
Discharge medications						
Aspirin	98.9 (651/658)	98.8 (245/248)	>0.99	98.9 (641/648)	99.3 (278/280)	0.73
$P2Y_{12}$ inhibitor	33.7 (223/661)	30.4 (76/250)	0.34	98.3 (639/650)	97.2 (273/281)	0.25
DAPT	33.4 (221/661)	28.8 (72/250)	0.18	97.4 (633/650)	96.1 (270/281)	0.29
Statin	92.6 (612/661)	92.0 (230/250)	0.77	96.0 (624/650)	97.5 (274/281)	0.25
Beta-blocker	92.7 (613/661)	92.0 (230/250)	0.71	83.1 (540/650)	83.6 (235/281)	0.84
ACE inhibitor or ARB	40.7 (269/661)	46.0 (115/250)	0.15	54.8 (154/281)	57.5 (374/650)	0.44

Values are % (n/N) or mean ± SD. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LMCA, left main coronary artery; PCI, percutaneous coronary intervention.

3-YEAR OUTCOMES. Clinical outcomes according to diabetes status and treatment group are shown in Table 4 and Figure 1. Compared with nondiabetic patients, diabetic patients had higher 3-year rates of the composite primary endpoint, including higher rates of all-cause death, cardiovascular death, MI, and IDR. The rates of the 3-year composite primary endpoint of death, stroke, or MI, or the secondary composite endpoint of death, stroke, MI, or IDR were not significantly different between CABG and PCI in either of the nondiabetic and diabetic cohorts. The 3-year rate of all-cause death was significantly higher after PCI compared with CABG in diabetic patients (13.6% vs. 8.0%; p = 0.046), but not

in nondiabetic patients (5.5% vs. 5.0%; p = 0.71). IDR rates were lower after CABG compared with PCI in both diabetic and nondiabetic patients, whereas graft occlusion or stent thrombosis rates were lower after PCI compared with CABG. There were no significant interactions between diabetes status and treatment for any of the 3-year study endpoints, including mortality.

Table 3. 30-Day Clinical Outcomes According to Diabetes Status and Revascularization Assignment.

	All (N = 1,904)			No Diabetes (n= 1,350)			Diabetes (n = 554)			
	No Diabetes (n = 1,350)	Diabetes (n = 554)	*p* Value	CABG (n = 688)	PCI (n = 662)	*p* Value	CABG (n = 268)	PCI (n = 286)	*p* Value	$p_{interaction}$
Death, stroke, or MI	6.0 (80)	7.5 (41)	0.24	7.2 (49)	4.7 (31)	0.06	9.8 (26)	5.3 (15)	0.05	0.61
Death, stroke, MI, or IDR	6.3 (84)	7.6 (42)	0.29	7.8 (53)	4.7 (31)	0.02	10.2 (27)	5.3 (15)	0.03	0.69
Death	0.9 (12)	1.3 (7)	0.46	0.9 (6)	0.9 (6)	0.96	1.5 (4)	1.1 (3)	0.63	0.68
Cardiovascular	0.8 (11)	1.3 (7)	0.36	0.7 (5)	0.9 (6)	0.73	1.5 (4)	1.1 (3)	0.63	0.58
Stroke	0.8 (10)	1.5 (8)	0.15	0.9 (6)	0.6 (4)	0.55	2.3 (6)	0.7 (2)	0.13	0.44
MI	4.9 (66)	5.5 (30)	0.65	6.1 (41)	3.8 (25)	0.06	6.8 (18)	4.2 (12)	0.20	0.98
Periprocedural	4.9 (65)	4.6 (25)	0.77	5.9 (40)	3.8 (25)	0.08	6.1 (16)	3.2 (9)	0.12	0.68
Spontaneous	0.1 (1)	0.9 (5)	0.003	0.1 (1)	0	0.32	0.8 (2)	1.1 (3)	0.72	0.99
All repeat revascularization	1.0 (13)	1.3 (7)	0.56	1.3 (9)	0.6 (4)	0.18	1.5 (4)	1.1 (3)	0.63	0.66
IDR	0.9 (12)	1.3 (7)	0.46	1.3 (9)	0.5 (3)	0.09	1.5 (4)	1.1 (3)	0.63	0.48
PCI	0.5 (7)	1.3 (7)	0.09	0.6 (4)	0.5 (3)	0.74	1.5 (4)	1.1 (3)	0.63	0.92
CABG	0.4 (5)	0	0.15	0.7 (5)	0	0.03	0	0	—	>0.99
Graft occlusion or stent thrombosis	0.7 (9)	0.9 (5)	0.59	1.2 (8)	0.2 (1)	0.02	1.1 (3)	0.7 (2)	0.59	0.26
Major adverse events*	15.3 (204)	15.1 (83)	0.92	23.1 (156)	7.3 (48)	<0.001	23.5 (62)	7.4 (21)	<0.001	0.97

Values are % (n) of Kaplan-Meier time-to-first event estimates. *The composite rate of death, stroke, myocardial infarction, TIMI major or minor bleeding, transfusion >2 U of blood, major arrhythmia (supraventricular tachycardia requiring cardioversion, ventricular tachycardia or fibrillation requiring treatment, or bradyarrhythmia requiring temporary or permanent pacemaker), ischemia-driven revascularization, any unplanned surgery or therapeutic radiologic procedure, renal failure (serum creatinine increase by >0.5 mg/dl from baseline or need for dialysis), sternal wound dehiscence, infection requiring antibiotics, or prolonged intubation (>48 h). IDR, ischemia-driven revascularization; MI, myocardial infarction; other abbreviations as in Table 2.

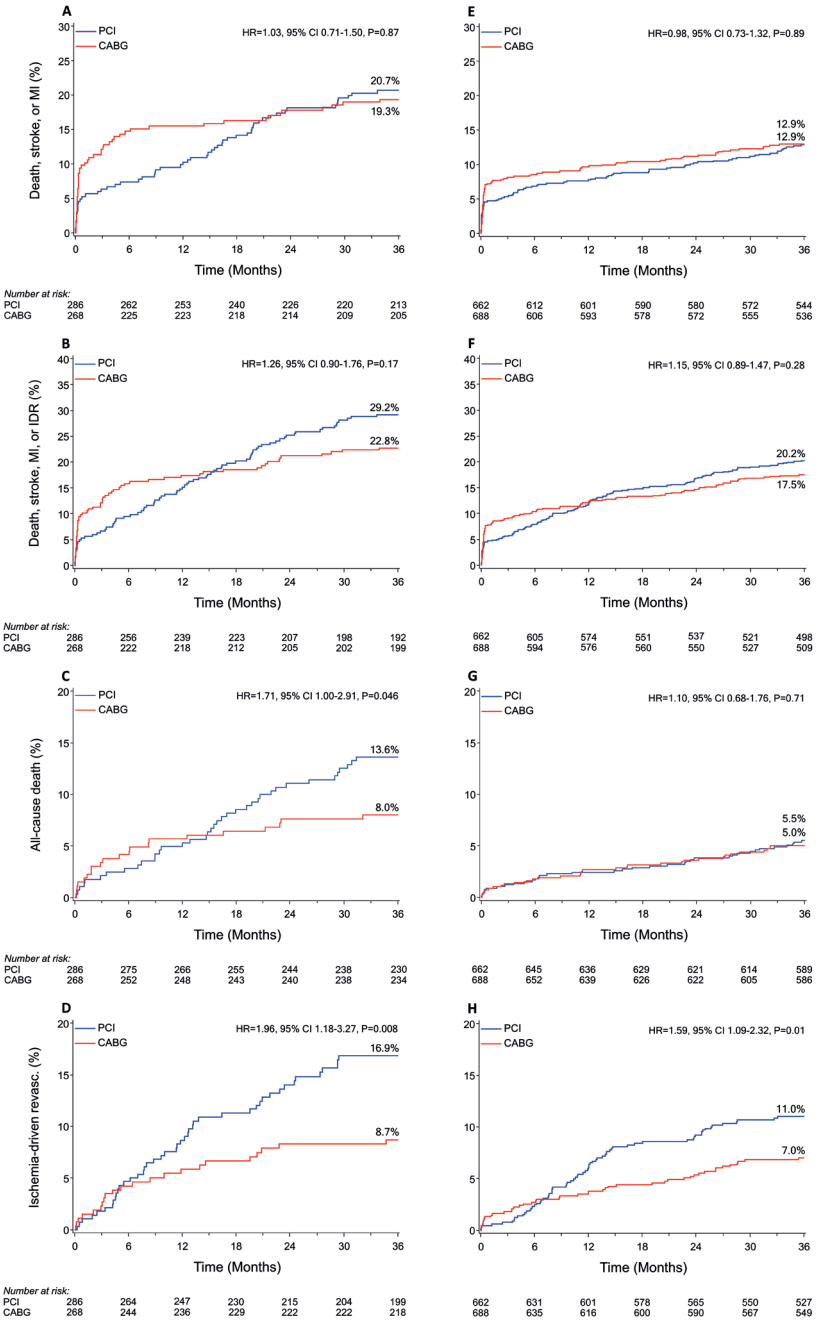


Figure 1. 3-Year Outcomes of PCI Versus CABG in Diabetic and Nondiabetic Patients. Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or myocardial infarction (MI); the composite endpoint of all-cause death, stroke, MI, or ischemia-driven repeat revascularization; all-cause death; and IDR in patients with **(A to D)** and without **(E to H)** diabetes. p Values are by log-rank test. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; IDR, ischemia-driven revascularization; PCI, percutaneous coronary intervention.

IMPACT OF INSULIN TREATMENT. Among diabetic patients, insulin use was associated with greater 3year rates of MI and IDR (Supplemental Table 3). The rate of the 3-year primary composite endpoint of death, stroke, or MI was similar after PCI and CABG in both insulin-treated and non–insulin-treated diabetic patients (Figure 2). There were no significant interactions between insulin use, revascularization modality, and 3-year outcomes among diabetic patients (Supplemental Table 3).

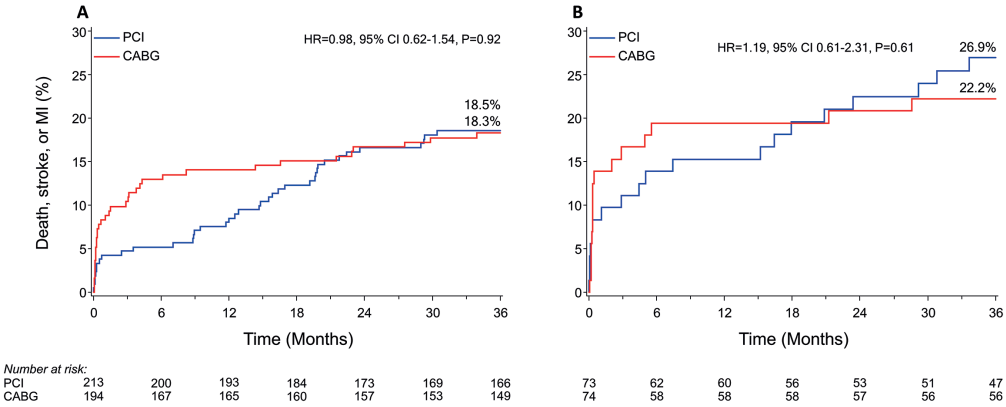


Figure 2. 3-Year Outcomes in Patients with Diabetes Stratified by Insulin Treatment. Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or MI among non–insulin-treated **(A)** and insulin-treated **(B)** patients. The p values are by log-rank test. Abbreviations as in Figure 1.

SYNTAX SCORE SUBGROUPS. Analysis according to site-reported coronary complexity showed a stepwise increase in 3-year event rates with intermediate compared with low SYNTAX scores in diabetic patients, but similar event rates in nondiabetic patients (Figure 3, Supplemental Table 4). In patients with diabetes and low SYNTAX scores (0 to 22), no significant 3-year event rate differences were observed between CABG and PCI, except for IDR (7.8% vs. 17.0%, respectively; p = 0.02); however, 3-year mortality was lower after CABG compared with PCI among the 237 diabetic patients with intermediate SYNTAX scores (9.6% vs. 19.6%; p = 0.04). However, the interaction between low versus intermediate site-assessed SYNTAX score and revascularization modality for 3-year death in diabetic patients was not significant (p = 0.32). Among nondiabetic patients, rates of adverse events were not significantly different after PCI and CABG irrespective of SYNTAX scores. The results according to core lab adjudication were similar to those from the site-reported analysis (Supplemental Table 5, Supplemental Figure 1).

MULTIVARIABLE ANALYSIS. As shown in Supplemental Tables 6 and 7, diabetes was an independent predictor for the composite endpoint of death, stroke, or MI after both CABG (hazard ratio (HR): 1.55; 95% confidence interval (CI): 1.04 to 2.31; p = 0.03) and PCI (HR: 1.53; 95% CI: 1.04 to 2.26; p = 0.03). Diabetes was also an independent predictor of stroke after CABG and all-cause death after PCI.

Table 4. 3-Year Clinical Outcomes According to Diabetes Status and Revascularization Assignment.

	All (N = 1,904)			No Diabetes (n = 1,350)			Diabetes (n = 554)			
	No Diabetes (n = 1,350)	Diabetes (n = 554)	*p* Value	CABG (n = 688)	PCI (n = 662)	*p* Value	CABG (n = 268)	PCI (n = 286)	*p* Value	$p_{interaction}$
Death, stroke, or MI	12.9 (170)	20.0 (109)	<0.001	12.9 (86)	12.9 (84)	0.89	19.3 (51)	20.7 (58)	0.87	0.82
Death, stroke, MI, or IDR	18.9 (248)	26.1 (142)	<0.001	17.5 (116)	20.2 (132)	0.28	22.8 (60)	29.2 (82)	0.17	0.65
Death	5.3 (69)	10.9 (59)	<0.001	5.0 (33)	5.5 (36)	0.71	8.0 (21)	13.6 (38)	0.046	0.22
Cardiovascular	3.1 (41)	6.2 (33)	0.002	3.1 (20)	3.2 (21)	0.85	5.4 (14)	7.0 (19)	0.48	0.68
Stroke	2.3 (30)	3.6 (19)	0.11	2.3 (15)	2.3 (15)	0.99	5.1 (13)	2.3 (6)	0.08	0.17
MI	7.3 (96)	10.5 (56)	0.03	7.5 (50)	7.1 (46)	0.73	10.8 (28)	10.3 (28)	0.76	0.99
Periprocedural	5.0 (67)	4.7 (26)	0.80	6.1 (41)	4.0 (26)	0.09	6.1 (16)	3.5 (10)	0.17	0.81
Spontaneous	2.4 (30)	6.4 (33)	<0.001	1.6 (10)	3.2 (20)	0.06	5.6 (14)	7.2 (19)	0.50	0.38
All repeat revascularizations	9.2 (117)	13.1 (68)	0.01	7.0 (45)	11.3 (72)	0.008	9.1 (23)	16.9 (45)	0.01	0.68
IDR	9.0 (115)	12.9 (67)	0.01	7.0 (45)	11.0 (70)	0.01	8.7 (22)	16.9 (45)	0.008	0.51
PCI	7.6 (97)	11.1 (58)	0.01	6.1 (39)	9.1 (58)	0.04	8.3 (21)	13.8 (37)	0.058	0.77
CABG	2.0 (26)	2.2 (11)	0.89	0.9 (6)	3.1 (20)	0.005	0.4 (1)	3.8 (10)	0.009	0.37
Graft occlusion or stent thrombosis	2.6 (34)	4.0 (21)	0.12	4.8 (31)	0.5 (3)	<0.001	6.7 (17)	1.5 (4)	0.002	0.32

Values are % (n) of Kaplan-Meier time-to-first event estimates. Abbreviations as in Tables 2 and 3.

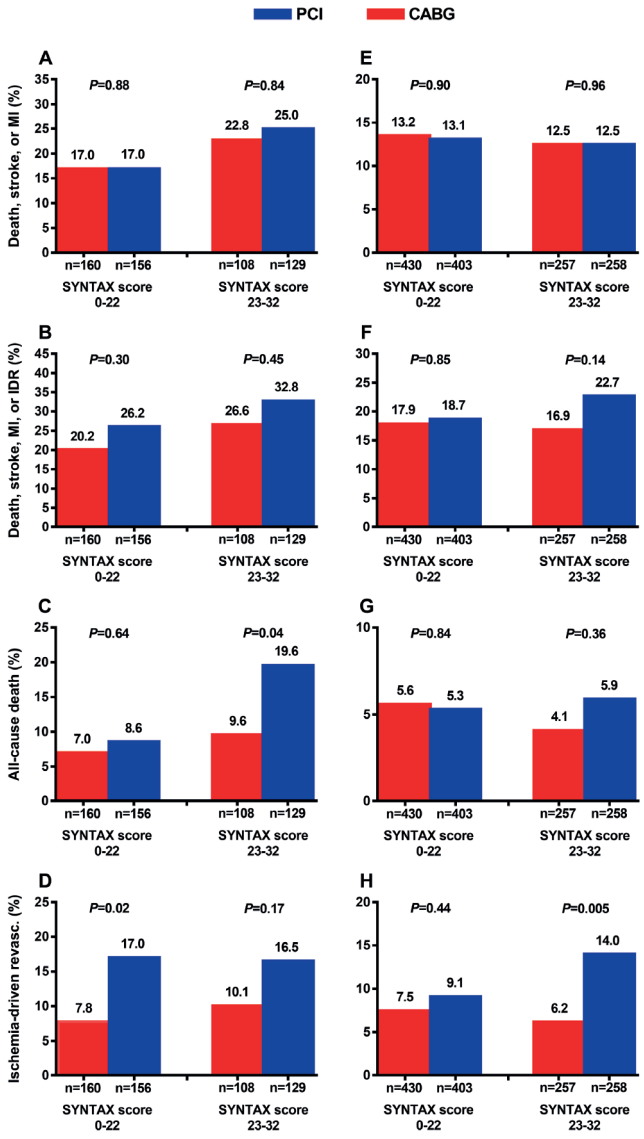


Figure 3. 3-Year Outcomes for Diabetic and Nondiabetic Patients According to Anatomic Lesion Complexity as Measured by the Site-Assessed SYNTAX Score. Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or MI; the composite endpoint of all-cause death, stroke, MI, or ischemia-driven repeat revascularization (IDR); all-cause death; and IDR in diabetic patients **(A to D)** and nondiabetic patients **(E to H)**. Treatment by SYNTAX score interactions in the diabetic and the nondiabetic groups: The composite endpoint of all-cause death, stroke, or MI (p_{int} = 0.81 and p_{int} = 0.98); the composite endpoint of all-cause death, stroke, MI, or IDR (p_{int} = 0.87 and p_{int} = 0.31); all-cause death (p_{int} = 0.32 and p_{int} = 0.40); and IDR (p_{int} = 0.63 and p_{int} = 0.10). p Values are by log-rank test. Rates are separated according to the sitereported SYNTAX score values, indicating low (0 to 22) and intermediate (23 to 32) anatomic lesion complexity. SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery; other abbreviations as in Figure 1.

DISCUSSION

The present pre-specified EXCEL substudy examined the impact of diabetes on clinical outcomes after PCI with EES versus CABG in patients with LMCAD and site-assessed low or intermediate SYNTAX scores (Central Illustration). Compared with nondiabetic patients, diabetic patients with LMCAD were at a nearly 2-fold higher risk for all-cause death, stroke, or MI at 3 years. There was no significant difference in the 3-year composite primary endpoint of death, stroke, or MI or the powered 3-year secondary endpoint of death, stroke, MI, or IDR after PCI or CABG either in the diabetic or nondiabetic strata. Thirty-day adverse events were significantly less after PCI compared with CABG both in diabetic and nondiabetic patients. Conversely, all-cause mortality at 3 years was greater after PCI compared with CABG among diabetic patients with higher site-assessed SYNTAX scores, although the interaction between site-assessed SYNTAX score and revascularization modality for 3-year death in diabetic patients was not significant. IDR at 3 years was higher with PCI, whereas graft failure or thrombosis rates were higher after CABG, both irrespective of diabetic status.

Our findings confirm that diabetes is a critical determinant of long-term outcomes after myocardial revascularization (3,4). Currently, no specific recommendation exists concerning the optimal revascularization strategy in diabetic patients with LMCAD (6). Given the clinical and anatomic complexity that is frequently present in this high-risk subgroup, the selection between CABG and PCI in diabetic patients requires careful consideration. Large-registry data show a substantial increase in the number of patients with diabetes and LMCAD undergoing PCI over the last 20 years, although outcomes data are scarce (11). Before the present report, comparative effectiveness data for PCI with drug-eluting stents (DES) versus CABG in diabetic patients were limited to small subgroup analyses from clinical trials. In a pooled analysis of individual patient data from the PRECOMBAT (Bypass Surgery Versus Angioplasty Using SirolimusEluting Stent in Patients With Left Main Coronary Artery Disease) and the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trials, Cavalcante et al. (12) found no difference in the occurrence of major adverse events between CABG and PCI with first-generation DES in LMCAD patients with or without diabetes at 5-year follow-up. The present results in which second-generation EES and contemporary CABG techniques were evaluated are consistent with these findings and indicate that both revascularization strategies result in comparable rates of major adverse events at 3 years.

Although PCI resulted in substantially fewer major adverse events at 30 days in both diabetic and nondiabetic patients, an important consideration affecting the selection of revascularization procedure is long-term survival. In this regard, a large propensity-matched analysis of 4,048 patient-pairs from the New York State outcomes registries suggested that the apparent survival benefit of CABG over PCI in diabetic patients in the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) and SYNTAX trials (3,4) might be lost when PCI was performed with EES (13); however, registries are particularly sensitive to the occurrence of selection bias, and these results must be interpreted with caution (14). Among the 554 diabetic patients randomized in the EXCEL trial, a significant difference in mortality between CABG and PCI was observed in those with higher SYNTAX scores; however, the EXCEL trial was not powered for mortality in the entire population, let alone the diabetic subgroup, and no interaction was noted between diabetic status, revascularization, and 3-year mortality. In a recently published pooled analysis of individual randomized patient data (15) from the SYNTAX, PRECOMBAT, EXCEL, and NOBLE (PCI vs. CABG in the Treatment of Unprotected Left Main Stenosis) trials (8,16–18), there was no significant difference in 5-year mortality after treatment of 4,478 patients with LMCAD with PCI versus CABG (10.7% vs. 10.5%; HR: 1.07; 95% CI: to 1.33; p = 0.52), either in patients with (n = 1,120; HR: 1.34; 95% CI: 0.93 to 1.31) or without (n = 3,358; HR: 0.94; 95% CI: 0.72 to 1.23) diabetes. In this analysis, CABG did, however, result in superior survival to PCI in diabetic patients with multivessel disease (but without LMCA involvement), again suggesting that in general patients with diabetes and complex CAD may preferentially benefit by CABG.

Finally, despite the fact that evidence supports the recommendation of increasing use of BIMA grafts during CABG in diabetic patients who are at low risk of deep sternal wound infection (6,19,20), rates of BIMA usage are still relatively low (only 19.6% of diabetic patients in the present trial). No significant differences in sternal wound dehiscence were observed in diabetic patients treated with a single internal mammary artery versus BIMA in the EXCEL trial. It is also noteworthy that adherence rates to guideline-directed medication therapy after CABG have reached 90% in the EXCEL trial (21) but remain lower than after PCI. Of note, approximately onethird of CABG patients were discharged on dual antiplatelet therapy, which, although less than after PCI, represents a higher percentage than in some other studies. This may reflect appropriate use after CABG in patients presenting with acute coronary syndromes, as well as the potential for dual antiplatelet therapy to enhance graft patency (22), the topic of several ongoing randomized controlled trials (Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis

(TARGET), NCT02053909; Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery (POPular CABG), NCT02352402; Study Comparing Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG (TiCAB), NCT01755520). Optimizing guidelinedirected medication therapy after both CABG and PCI is essential for patients to derive the most benefits from revascularization.

STUDY LIMITATIONS. Although randomization was stratified by diabetes status, and the diabetes subgroup analysis was pre-specified in the EXCEL trial design, the present study was not powered to detect a difference in the primary endpoint of death, stroke, or MI between PCI and CABG in the diabetic cohort, and secondary outcome measures were not adjusted for multiple comparisons. Hence, the results of the present study should be interpreted as hypothesisgenerating only, and further investigation in dedicated trials of diabetic patients are warranted (23,24). In addition, the EXCEL trial enrolled patients with LMCAD and site-assessed low or intermediate SYNTAX scores who were eligible to undergo both PCI and CABG. Therefore, these findings cannot be extrapolated either to patients with unacceptable high surgical risk or patients with coronary anatomy unsuitable for PCI. A major focus of diabetes management is optimal glycemic control. Recently, the use of gliflozins has been shown to reduce the risk of major cardiovascular events in patients with type 2 diabetes (25). Unfortunately, the use of specific oral hypoglycemic agents and data on long-term glycemic control were not collected in the present study. Finally, follow-up in the EXCEL trial is complete only through 3 years; longer-term surveillance is necessary to examine whether additional differences emerge over time.

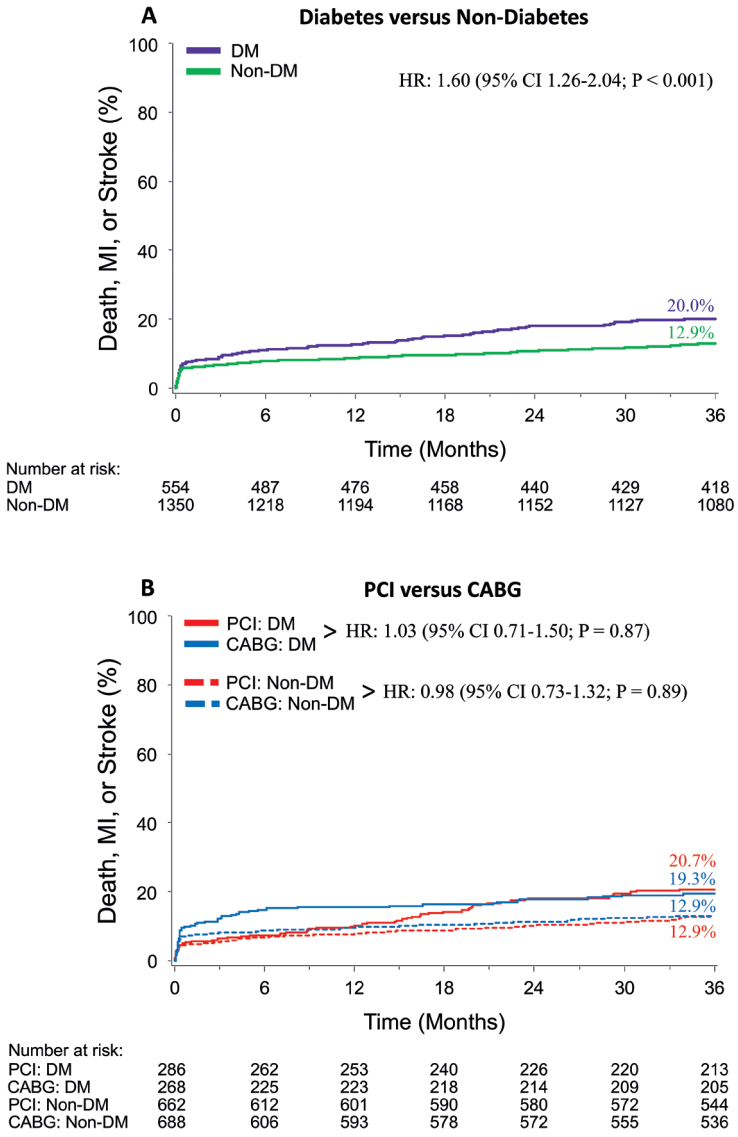
CONCLUSIONS

In the large-scale EXCEL trial, among both diabetic and nondiabetic patients with LMCAD and siteassessed low-to-intermediate (<=32) SYNTAX scores, PCI using EES and CABG resulted in similar rates of the primary composite endpoint of death, stroke, or MI at 3-year follow-up, although fewer adverse events at 30 days occurred after PCI. For diabetic patients with LMCAD and relatively noncomplex coronary anatomy, PCI may be a reasonable approach, whereas CABG should be considered for diabetic patients with more complex CAD.

CLINICAL PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with diabetes mellitus and left main coronary artery disease (LMCAD) undergoing myocardial revascularization are at higher risk of mortality and major adverse events than those without diabetes. In a randomized trial, there was no difference in the 3-year composite endpoint of all-cause death, stroke, or myocardial infarction between PCI and CABG, irrespective of baseline diabetes status.

TRANSLATIONAL OUTLOOK: While CABG remains the standard of care for diabetic patients with complex CAD, further studies are needed to ascertain the characteristics of patients with diabetes who can be appropriately managed by percutaneous intervention.



Central illustration. Impact of Diabetes Mellitus on 3-Year Outcomes After Left Main Revascularization. The incidence rates of the primary composite endpoint of death, stroke, or MI among diabetic and non-diabetic patients **(A)** and according to the type of revascularization procedure **(B)** are shown. Over the 3-year follow-up period, PCI with EES compared with CABG was associated with similar risk of the primary composite endpoint among both diabetic and nondiabetic patients. CABG, coronary artery bypass grafting; CI, confidence interval; DM, diabetes mellitus; EES, everolimus-eluting stents; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Rates of medication use during the 3-year follow-up period.

	CABG (n=956)			PCI (n=948)			CABG vs. PCI	
	No diabetes (n=688)	Diabetes (n=268)	P-Value	No diabetes (n=662)	Diabetes (n=286)	P-Value	P-Value No Diabetes	P-Value Diabetes
Aspirin								
Discharge	98.9 (651/658)	98.8 (245/248)	0.90	98.9 (641/648)	99.3 (278/280)	0.57	>0.99	0.55
6 months	97.7 (644/659)	96.8 (243/251)	0.44	97.7 (631/646)	97.8 (268/274)	0.93	>0.99	0.48
12 months	96.3 (629/653)	96.4 (239/248)	0.94	95.8 (614/641)	98.9 (264/267)	0.017	0.65	0.059
24 months	95.3 (591/620)	96.2 (229/238)	0.57	94.4 (586/621)	99.2 (243/245)	0.002	0.47	0.027
36 months	95.5 (569/596)	95.3 (224/235)	0.90	92.7 (559/603)	98.7 (230/233)	<0.001	0.039	0.032
P2Y12 inhibitor								
Discharge	33.7 (223/661)	30.4 (76/250)	0.34	98.3 (639/650)	97.2 (273/281)	0.28	<0.001	<0.001
6 months	27.8 (184/662)	28.3 (72/254)	0.88	97.4 (631/648)	97.1 (267/275)	0.79	<0.001	<0.001
12 months	25.2 (165/656)	26.0 (65/250)	0.80	83.8 (539/643)	84.3 (226/268)	0.85	<0.001	<0.001
24 months	21.8 (136/623)	24.6 (59/240)	0.38	69.2 (431/623)	72.0 (177/246)	0.42	<0.001	<0.001
36 months	21.0 (126/599)	24.9 (59/237)	0.22	65.8 (398/605)	69.2 (162/234)	0.35	<0.001	<0.001
DAPT								
Discharge	33.4 (221/661)	28.8 (72/250)	0.18	97.4 (633/650)	96.1 (270/281)	0.28	<0.001	<0.001
6 months	26.7 (177/662)	27.2 (69/254)	0.88	95.4 (618/648)	94.5 (260/275)	0.56	<0.001	<0.001
12 months	23.5 (154/656)	25.2 (63/250)	0.59	80.6 (518/643)	82.8 (222/268)	0.44	<0.001	<0.001
24 months	19.6 (122/623)	23.3 (56/240)	0.23	64.5 (402/623)	70.7 (174/246)	0.08	<0.001	<0.001
36 months	18.7 (112/599)	23.6 (56/237)	0.11	60.5 (366/605)	67.5 (158/234)	0.06	<0.001	<0.001
Statin								
Discharge	92.6 (612/661)	92.0 (230/250)	0.76	96.0 (624/650)	97.5 (274/281)	0.25	0.008	0.040
6 months	95.0 (626/659)	93.7 (237/253)	0.44	96.6 (624/646)	97.5 (268/275)	0.47	0.15	0.032
12 months	96.3 (626/650)	94.0 (233/248)	0.13	96.7 (621/642)	97.4 (261/268)	0.58	0.70	0.055
24 months	96.8 (602/622)	93.7 (24/239)	0.039	96.9 (603/622)	97.2 (239/246)	0.82	0.92	0.064
36 months	97.0 (580/598)	93.2 (220/236)	0.012	96.7 (585/605)	97.4 (228/234)	0.60	0.76	0.032
Beta-blocker								
Discharge	92.7 (613/661)	92.0 (230/250)	0.72	83.1 (540/650)	83.6 (235/281)	0.85	<0.001	0.003
6 months	94.4 (624/661)	92.9 (234/252)	0.39	84.5 (546/646)	86.1 (236/274)	0.54	<0.001	0.011
12 months	94.5 (620/656)	93.5 (232/248)	0.56	85.2 (546/641)	86.5 (231/267)	0.61	<0.001	0.008
24 months	95.3 (593/622)	93.3 (223/239)	0.24	85.0 (528/621)	86.2 (212/246)	0.65	<0.001	0.010
36 months	94.5 (566/599)	92.8 (219/236)	0.35	85.6 (516/603)	87.6 (205/234)	0.45	<0.001	0.057

Supplemental Table 1. Continued.

ACEI or ARB								
Discharge	40.7 (269/661)	46.0 (115/250)	0.15	57.5 (374/650)	54.8 (154/281)	0.45	<0.001	0.043
6 months	47.9 (311/649)	56.2 (141/251)	0.026	61.3 (396/646)	58.8 (160/272)	0.48	<0.001	0.55
12 months	52.0 (333/641)	60.8 (149/245)	0.019	62.7 (400/638)	61.9 (164/265)	0.82	<0.001	0.80
24 months	53.9 (332/616)	61.3 (146/238)	0.051	64.7 (400/618)	63.9 (156/244)	0.83	<0.001	0.55
36 months	54.6 (325/595)	64.4 (150/233)	0.010	64.4 (389/604)	65.8 (152/231)	0.70	<0.001	0.75

Values are presented as % (n/N). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Supplemental Table 2. Incidence and the 30-day outcome of acute renal failure.

	All (n=1904)			No Diabetes (n=1350)			Diabetes (n=554)			
	No diabetes (n = 1350)	Diabetes (n = 554)	P Value	CABG (n = 688)	PCI (n = 662)	P Value	CABG (n = 268)	PCI (n = 286)	P Value	$P_{interaction}$
Acute Renal Failure	1.1 (15)	2.7 (15)	0.01	1.9 (13)	0.3 (2)	0.005	4.1 (11)	1.4 (4)	0.050	0.44
New requirement for dialysis	0.6 (8)	1.6% (9)	0.03	0.9 (6)	0.3 (2)	0.29	3.0 (8)	0.4 (1)	0.02	0.41
Hemodialysis	0.4 (5)	0.9 (5)	0.17	0.6 (4)	0.2 (1)	0.37	1.5 (4)	0.4 (1)	0.20	0.94
CVVH	0.3 (3)	0.7 (4)	0.24	0.3 (2)	0.3 (2)	1.00	1.5 (4)	0.0 (0)	0.054	0.95
Outcomes in ARF patients										
Death, stroke, or MI	20.0 (3)	33.0 (5)	0.47	15.4 (2)	50.0 (1)	0.15	45.5 (5)	0.0 (0)	0.13	>0.99
Death, stroke, MI, or IDR	20.0 (3)	33.3 (5)	0.46	15.4 (2)	50.0 (1)	0.15	45.5 (5)	0.0 (0)	0.13	>0.99
Death	6.7 (1)	6.7 (1)	0.98	7.7 (1)	0.0 (0)	0.69	9.1 (1)	0.0 (0)	0.55	1.00
Stroke	0.0 (0)	13.9 (2)	0.16	0.0 (0)	0.0 (0)	NA	19.2 (2)	0.0 (0)	0.37	>0.99
MI	20.0 (3)	13.3 (2)	0.62	15.4 (2)	50.0 (1)	0.15	18.2 (2)	0.0 (0)	0.38	>0.99
All repeat revascularizations	7.1 (1)	13.3 (2)	0.56	8.3 (1)	0.0 (0)	0.68	18.2 (2)	0.0 (0)	0.38	>0.99
IDR	7.1 (1)	13.3 (2)	0.56	8.3 (1)	0.0 (0)	0.68	18.2 (2)	0.0 (0)	0.38	>0.99
PCI	7.1 (1)	13.3 (2)	0.56	8.3 (1)	0.0 (0)	0.68	18.2 (2)	0.0 (0)	0.38	>0.99
CABG	0.0 (0)	0.0 (0)	NA	0.0 (0)	0.0 (0)	NA	0.0 (0)	0.0 (0)	NA	NA
Graft occlusion or stent thrombosis	7.1 (1)	6.7 (1)	>0.99	8.3 (1)	0.0 (0)	0.68	9.1 (1)	0.0 (0)	0.55	1.00

Values are Kaplan-Meier time-to-first event estimates expressed as % (n). CABG, coronary artery bypass grafting; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Table 3. Three-Year Clinical Outcomes in Diabetic Patients According to Insulin Treatment and Revascularization Assignment.

	All Diabetes (n = 554)			No Insulin (n = 407)			Insulin (n = 147)			
	No insulin (n = 407)	Insulin (n = 147)	P Value	CABG (n = 194)	PCI (n = 213)	P Value	CABG (n = 74)	PCI (n = 73)	P Value	$P_{interaction}$
Death, stroke, or MI	18.4 (74)	24.5 (35)	0.10	18.3 (35)	18.5 (39)	0.92	22.2 (16)	26.9 (19)	0.61	0.63
Death, stroke, MI, or IDR	23.7 (95)	32.8 (47)	0.03	20.9 (40)	26.2 (55)	0.31	27.8 (20)	38.2 (27)	0.29	0.77
Death	11.0 (44)	10.6 (15)	0.92	7.8 (15)	13.8 (29)	0.07	8.4 (6)	13.0 (9)	0.42	0.82
Cardiovascular	5.6 (22)	7.9 (11)	0.34	5.3 (10)	5.9 (12)	0.82	5.7 (4)	10.2 (7)	0.35	0.52
Stroke	3.4 (13)	4.4 (6)	0.59	4.8 (9)	2.0 (4)	0.12	5.7 (4)	3.2 (2)	0.43	0.83
MI	8.6 (34)	15.8 (22)	0.02	9.1 (17)	8.3 (17)	0.73	15.4 (11)	16.4 (11)	0.95	0.81
Periprocedural	4.0 (16)	6.9 (10)	0.15	5.2 (10)	2.8 (6)	0.23	8.3 (6)	5.5 (4)	0.56	0.77
Spontaneous	4.7 (18)	11.1 (15)	0.009	3.9 (7)	5.5 (11)	0.46	10.1 (7)	12.3 (8)	0.78	0.77
All repeat revascularizations	11.2 (43)	18.5 (25)	0.03	7.6 (14)	14.4 (29)	0.04	13.1 (9)	24.3 (16)	0.14	0.92
IDR	10.9 (42)	18.5 (25)	0.02	7.1 (13)	14.4 (29)	0.02	13.1 (9)	24.3 (16)	0.14	0.81
PCI	9.9 (38)	14.8 (20)	0.11	7.1 (13)	12.3 (25)	0.09	11.6 (8)	18.3 (12)	0.37	0.77
CABG	1.6 (6)	3.8 (5)	0.13	0	3.1 (6)	0.02	1.5 (1)	6.1 (4)	0.17	0.99
Graft occlusion or stent thrombosis	2.8 (11)	7.3 (10)	0.02	4.9 (9)	1.0 (2)	0.02	11.7 (8)	2.9 (2)	0.053	0.85

Values are Kaplan-Meier time-to-first event estimates expressed as % (n). CABG, coronary artery bypass grafting; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Table 4. Three-Year Clinical Outcomes According to Diabetes Status, Site-Reported SYNTAX Score, and Revascularization.

	SYNTAX Score 0-22			SYNTAX Score 23-32		
	CABG	PCI	P Value	CABG	PCI	P Value
Diabetic cohort	(n=160)	(n=156)		(n=108)	(n=129)	
Death, stroke, or MI	17.0 (27)	17.0 (26)	0.88	22.8 (24)	25.0 (32)	0.84
Death, stroke, MI, or IDR	20.2 (32)	26.2 (40)	0.30	26.6 (28)	32.8 (42)	0.45
Death	7.0 (11)	8.6 (13)	0.64	9.6 (10)	19.6 (25)	0.04
Cardiovascular	4.5 (7)	2.7 (4)	0.39	6.8 (7)	12.1 (15)	0.19
Stroke	5.8 (9)	2.1 (3)	0.09	2.5 (3)	4.0 (4)	0.54
MI	7.7 (12)	9.5 (14)	0.66	15.5 (16)	11.1 (14)	0.34
Periprocedural	3.1 (5)	1.3 (2)	0.27	10.5 (11)	6.2 (8)	0.26
Spontaneous	5.3 (8)	8.2 (12)	0.34	6.1 (6)	5.8 (7)	0.92
All repeat revascularization	8.5 (13)	17.0 (25)	0.04	10.1 (10)	16.5 (20)	0.17
IDR	7.8 (12)	17.0 (25)	0.02	10.1 (10)	16.5 (20)	0.17
PC	7.1 (11)	12.9 (19)	0.12	10.1 (10)	14.8 (18)	0.29
CABG	0.7 (1)	4.1 (6)	0.053	0	3.4 (4)	0.07
Graft occlusion or stent thrombosis	7.2 (11)	2.0 (3)	0.03	5.9 (6)	0.8 (1)	0.03
Non-diabetic cohort	(n=430)	(n=403)		(n=257)	(n=258)	
Death, stroke, or MI	13.2 (55)	13.1 (52)	0.90	12.5 (31)	12.5 (32)	0.96
Death, stroke, MI, or IDR	17.9 (74)	18.7 (74)	0.85	16.9 (42)	22.7 (58)	0.14
Death	5.6 (23)	5.3 (21)	0.84	4.1 (10)	5.9 (15)	0.36
Cardiovascular	3.7 (15)	3.1 (12)	0.62	2.1 (5)	3.5 (9)	0.31
Stroke	2.3 (9)	2.3 (9)	0.95	2.4 (6)	2.4 (6)	0.96
MI	7.7 (32)	7.1 (28)	0.72	7.2 (18)	7.1 (18)	0.93
Periprocedural	6.4 (27)	4.0 (16)	0.13	5.5 (14)	3.9 (10)	0.40
Spontaneous	1.5 (6)	3.1 (12)	0.14	1.6 (4)	3.2 (8)	0.27
All repeat revascularization	7.5 (30)	9.3 (36)	0.37	6.2 (15)	14.4 (36)	0.003
IDR	7.5 (30)	9.1 (35)	0.44	6.2 (15)	14.0 (35)	0.005
PCI	6.6 (26)	7.8 (30)	0.50	5.4 (13)	11.2 (28)	0.02
CABG	0.9 (4)	2.9 (11)	0.06	0.8 (2)	3.6 (9)	0.04
Graft occlusion or stent thrombosis	4.7 (19)	0.5 (2)	<0.001	5.0 (12)	0.4 (1)	0.002

Values are Kaplan-Meier time-to-event estimates expressed as % (n). CABG, coronary artery bypass grafting; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Table 5. Three-Year Clinical Outcomes According to Diabetes Status, Core Lab SYNTAX Score, and Revascularization.

	SYNTAX score 0-22			SYNTAX Score 23-32			SYNTAX score ≥33		
	CABG	PCI	P Value	CABG	PCI	P Value	CABG	PCI	P Value
Diabetic cohort	(n=94)	(n=73)		(n=99)	(n=135)		(n=70)	(n=66)	
Death, stroke, or MI	16.2 (15)	14.1 (10)	0.69	24.7 (24)	23.0 (31)	0.61	14.5 (10)	20.2 (13)	0.48
Death, stroke, MI or IDR	21.6 (20)	19.8 (14)	0.72	26.8 (26)	33.4 (45)	0.46	17.4 (12)	27.9 (18)	0.20
Death	8.7 (8)	5.7 (4)	0.44	9.3 (9)	16.4 (22)	0.14	5.8 (4)	15.8 (10)	0.07
Cardiovascular	6.6 (6)	1.5 (1)	0.11	4.2 (4)	8.3 (11)	0.22	5.8 (4)	10.0 (6)	0.41
Stroke	6.6 (6)	1.4 (1)	0.10	4.3 (4)	2.4 (3)	0.43	4.4 (3)	3.4 (2)	0.71
MI	5.6 (5)	9.9 (7)	0.29	13.6 (13)	10.1 (13)	0.33	11.6 (8)	7.9 (5)	0.45
Periprocedural	2.2 (2)	4.1 (3)	0.45	7.2 (7)	3.0 (4)	0.14	8.7 (6)	3.0 (2)	0.17
Spontaneous	3.5 (3)	5.9 (4)	0.48	7.5 (7)	7.2 (9)	0.83	4.5 (3)	6.5 (4)	0.61
All repeat revascularization	7.9 (7)	11.7 (8)	0.48	10.8 (10)	21.3 (27)	0.06	7.5 (5)	12.8 (8)	0.31
IDR	7.9 (7)	11.7 (8)	0.48	10.8 (10)	21.3 (27)	0.06	6.1 (4)	12.8 (8)	0.17
PCI	6.7 (6)	8.8 (6)	0.70	10.8 (10)	18.1 (23)	0.18	6.1 (4)	11.2 (7)	0.27
CABG	1.2 (1)	2.9 (2)	0.44	0	4.8 (6)	0.04	0	1.6 (1)	0.30
Graft occlusion or stent thrombosis	5.7 (5)	1.5 (1)	0.16	7.6 (7)	1.6 (2)	0.03	7.4 (5)	0	0.03
Nondiabetic cohort	(n=270)	(n=221)		(n=246)	(n=256)		(n=146)	(n=163)	
Death, stroke, or MI	12.3 (32)	9.2 (20)	0.21	13.4 (32)	14.7 (37)	0.69	14.0 (20)	14.8 (24)	0.89
Death, stroke, MI, or IDR	18.6 (48)	15.1 (33)	0.23	18.9 (45)	22.7 (57)	0.32	14.0 (20)	24.0 (39)	0.04
Death	4.7 (12)	3.7 (8)	0.55	5.1 (12)	6.8 (17)	0.44	5.7 (8)	6.2 (10)	0.84
Cardiovascular	2.4 (6)	1.8 (4)	0.69	3.4 (8)	4.0 (10)	0.73	3.6 (5)	4.4 (7)	0.72
Stroke	2.0 (5)	1.4 (3)	0.61	2.6 (6)	2.4 (6)	0.91	1.4 (2)	3.8 (6)	0.21
MI	6.9 (18)	5.1 (11)	0.35	7.5 (18)	8.4 (21)	0.72	9.2 (13)	7.5 (12)	0.58
Periprocedural	5.6 (15)	0.9 (2)	0.005	5.8 (14)	5.9 (15)	0.91	7.7 (11)	4.3 (7)	0.22
Spontaneous	1.2 (3)	4.2 (9)	0.05	1.7 (4)	2.5 (6)	0.59	2.2 (3)	3.2 (5)	0.59
All repeat revascularization	7.6 (19)	9.7 (21)	0.45	8.7 (20)	11.8 (29)	0.25	2.9 (4)	14.1 (22)	<0.001
IDR	7.6 (19)	9.3 (20)	0.56	8.7 (20)	11.4 (28)	0.31	2.9 (4)	14.1 (22)	<0.001
PCI	7.2 (18)	6.5 (14)	0.74	7.1 (16)	10.2 (25)	0.19	2.2 (3)	12.2 (19)	0.001
CABG	0.4 (1)	3.7 (8)	0.01	1.7 (4)	2.9 (7)	0.42	0.7 (1)	3.2 (5)	0.14
Graft occlusion or stent thrombosis	4.4 (11)	0.9 (2)	0.02	5.6 (13)	0.4 (1)	<0.001	2.9 (4)	0	0.03

Values are Kaplan-Meier time-to-event estimates expressed as % (n); log-rank p-value. CABG, coronary artery bypass grafting; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Table 6. Independent Predictors of Adverse Events in the CABG Cohort.

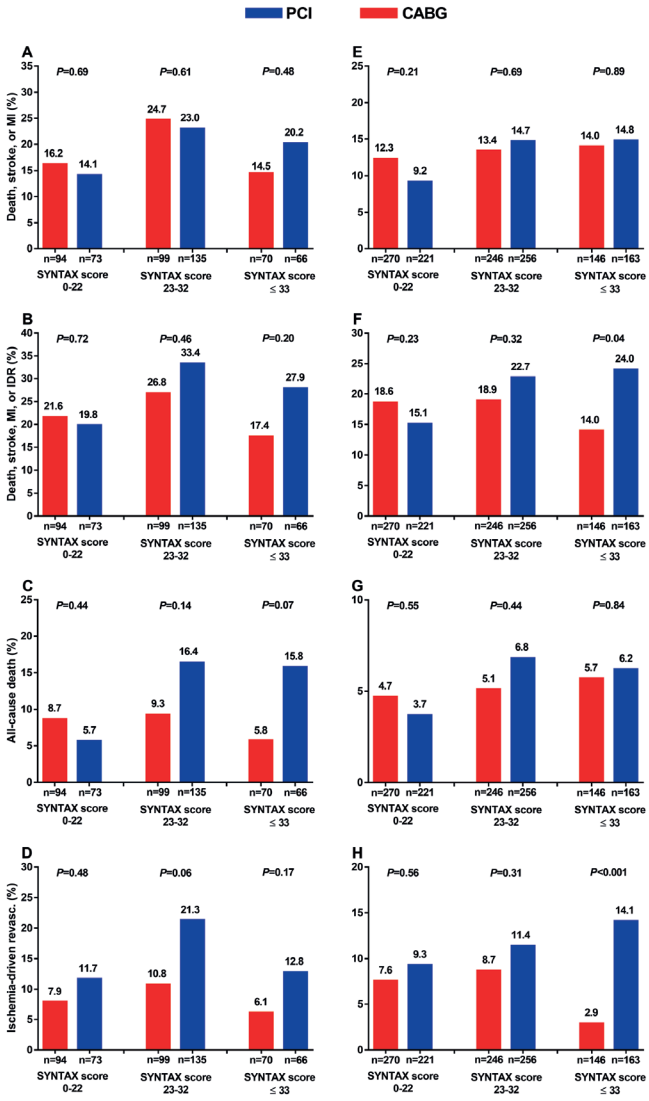
	Hazard Ratio (95% Confidence Interval)	P Value
Death, stroke, or MI		
Diabetes versus non-diabetes	1.55 (1.04-2.31)	0.03
Hypertension treated with medication	1.67 (1.02-2.72)	0.04
Death, stroke, MI, or IDR		
Hyperlipidemia treated with medication	0.66 (0.46-0.94)	0.02
All-cause death		
Current smoker	2.30 (1.11-4.79)	0.03
Left ventricular ejection fraction (%)	0.96 (0.94-0.99)	0.01
MI		
Age	0.96 (0.94-0.99)	0.009
Recent MI	1.84 (1.01-3.37)	0.048
Hypertension treated with medication	2.19 (1.14-4.18)	0.02
Hyperlipidemia treated with medication	0.56 (0.33-0.93)	0.03
Stroke		
Diabetes versus non-diabetes	3.38 (1.39-8.24)	0.007
IDR		
Age	0.96 (0.93-0.99)	0.01
Male	0.55 (0.30-0.99)	0.046
Hyperlipidemia treated with medication	0.30 (0.17-0.52)	<0.001

CABG, coronary artery bypass grafting; IDR, ischemia-driven revascularization; MI, myocardial infarction.

Supplemental Table 7. Independent predictors of adverse events in the PCI cohort.

	Hazard Ratio (95% Confidence Interval)	P Value
Death, stroke, or MI		
Diabetes versus non-diabetes	1.53 (1.04-2.26)	0.03
Age	1.03 (1.01-1.06)	0.008
Death, stroke, MI, or IDR		
Age	1.02 (1.00-1.04)	0.03
SYNTAX score	1.02 (1.00-1.03)	0.048
All-cause death		
Diabetes versus non-diabetes	2.51 (1.46-4.31)	<0.001
Age	1.06 (1.03-1.10)	<0.001
MI		
Body mass index	1.06 (1.01-1.11)	0.02
Stroke		
Male sex	0.34 (0.12-0.91)	0.03
Body mass index	0.87 (0.76-1.00)	0.04
IDR		
None identified	—	—

IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention.



Supplemental Figure 1. Three-Year Outcomes for Diabetic and Nondiabetic Patients According to Anatomic Lesion Complexity as Measured by the Core Laboratory-Assessed SYNTAX Score. Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or myocardial infarction (MI); the composite endpoint of all-cause death, stroke, MI, or ischemia-driven repeat revascularization (IDR); all-cause death; and IDR in diabetic patients **(A-D)** and non-diabetic patients **(E-H)**. Treatment by SYNTAX score interactions in the diabetic and the non-diabetic groups: The composite endpoint of all-cause death, stroke, or MI (P_{int}=0.64 and P_{int}=0.47); the composite endpoint of all-cause death, stroke, MI, or IDR (P_{int}=0.48 and P_{int}=0.056); all-cause death (P_{int}=0.20 and P_{int}=0.64); and IDR (P_{int}=0.82 and P_{int}=0.058). P values are from log-rank test. Rates are separated according to the site-reported SYNTAX score values, indicating low (0–22), intermediate (23–32), and high (≥33) anatomic lesion complexity. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Chapter 14

Influence of practice patterns on outcome among countries enrolled in the SYNTAX trial: 5-year results between percutaneous coronary intervention and coronary artery bypass grafting

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ABSTRACT

OBJECTIVES: To examine differences among participating countries in baseline characteristics, clinical practice, medication strategies and outcomes of patients randomized to coronary artery bypass grafting and percutaneous coronary intervention in the SYNTAX trial.

METHODS: In SYNTAX, centres in 18 different countries enrolled 1800 patients, of which 8 countries enrolled >_80 patients, what was projected to be a large enough sample size to be included in the analysis. Baseline characteristics, practice patterns and clinical outcomes were compared between the USA (n = 245), the UK (n = 267), Italy (n = 197), France (n = 208), Germany (n = 179), Netherlands (n = 148), Belgium (n = 91) and Hungary (n = 83). The remaining patients from other participating countries were pooled together (n = 382).

RESULTS: Five-year results demonstrated significantly different outcomes between countries. After adjustment, percutaneous coronary intervention patients in France had lower rates of major adverse cardiac and cerebrovascular events (hazard ratio (HR) = 0.60, 95% confidence interval (CI) 0.37–0.98), while the incidence of repeat revascularization was higher in Hungary (HR = 1.89, 95% CI 1.14–3.42). Coronary artery bypass grafting showed the lowest rate of repeat revascularization in the UK (HR = 0.32, 95% CI 0.12–0.85). There were numerous differences in the risk profile of patients between participating countries, as well as marked differences in surgical practice across countries in the use of blood cardioplegia (range 3.1–89.0%; P < 0.001), bilateral internal mammary artery usage (range 7.8–68.2%; P < 0.001) and off-pump procedures (range 3.9–44.4%; P < 0.001). Variation was also found for percutaneous coronary intervention in the number of implanted stents (range 4.0 ± 2.3 to 6.1 ± 2.6; P < 0.001) as well as for the entire stents length (range 69.0 ± 45.1 to 124.1 ± 60.9; P < 0.001). Remarkable differences were observed in the prescription of post-coronary artery bypass grafting medication in terms of acetylsalicylic acid (range 79.6–95.0%; P = 0.004), thienopyridine (6.8–31.1%; P < 0.001) and statins (41.3–89.1%; P < 0.001).

CONCLUSIONS: Patient characteristics and clinical patterns are significantly different between countries, resulting in significantly different 5-year outcomes. This article presents specific data that can further improve outcomes in each country.

INTRODUCTION

In order to expedite recruitment, there is a growing trend to involve centres from many different countries in large randomized clinical trials. As a consequence, participants can be enrolled more rapidly, the time span of trials is reduced, costs are less and the external validity of trial results is larger (1, 2). However, internal consistency may also be affected by differences in baseline characteristics, medical practice patterns and outcomes within participating countries or sites. Several recent reports have addressed the fundamental difficult issues of generalizability and cross-geographical clinical variations (1–3). Results from the PLATO trial suggested a significant treatment interaction of ticagrelor among patients with acute coronary syndromes enrolled in the USA or outside the USA, which was the result of differences in aspirin maintenance dose (4). Other studies have reported significant differences in baseline characteristics, practice patterns and clinical outcomes in subgroup analyses stratified according to site enrolment volume (5) and geographic region (6) among different clinical scenarios.

Findings from subgroup analyses may allow for a better understanding of risk–benefit ratios, can alter treatment recommendations and improve prognosis (7). In addition, these findings may identify areas in which practice varies between countries and may therefore generate awareness among outliers to improve patient care.

Coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) are both options for myocardial revascularization. Although many studies have been performed to aid decision-making of PCI versus CABG (8–10), no such data on geographic enrolment within a randomized controlled trial exists to date. We, therefore, evaluated differences in baseline characteristics, practice patterns and outcomes among countries that enrolled patients in the SYNTAX trial.

METHODS

Study design

The SYNTAX trial design has been described elsewhere (11). Briefly, it was an all-comers population of patients with *de novo* left main (LM) or 3-vessel disease, who were randomized to PCI with paclitaxel-eluting stents (n = 903) or CABG (n = 897) or went into nested PCI (n = 198) or CABG (n = 1077) registries (12). This analysis encompasses the randomized cohorts only.

Only those countries that had enrolled 80 or more patients in the randomized trial were analysed; this was the case in (i) the USA (*n* = 245; 13.6%), (ii) the UK (*n* = 267; 14.8%), (iii) Italy (*n* = 197; 10.9%), (iv) Germany (*n* = 179; 9.9%), (v) France (*n* = 208; 11.6%), (vi) the Netherlands (*n* = 148; 8.2%), (vii) Belgium (*n* = 91; 5.1%) and (viii) Hungary (*n* = 83; 4.6%). Patients from the remaining countries were pooled together in 1 group (Poland (*n* = 66; 3.7%), Sweden (*n* = 54; 3.0%), Spain (*n* = 53; 2.9%), Austria (*n* = 52; 2.9%), Czech Republic (*n* = 40; 2.2%), Latvia (*n* = 40; 2.2%), Denmark (*n* = 32; 1.8%), Finland (*n* = 24; 1.3%), Portugal (*n* = 13; 0.7%) and Norway (*n* = 8; 0.4%)), as recommended by Pocock *et al* (1). This study therefore consists of 9 groups of patients. Analyses of differences between countries were not pre-specified in this study. Therefore, the results of these subgroup analyses should be interpreted as 'hypothesis generating' only.

The institutional review board of all participating sites approved the protocol, which is consistent with the International Conference on Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki and all local regulations. Written consent was obtained from all participating patients before enrolment. The trial is registered on the National Institute of Health website with identifier NCT00114972.

End-points and definitions

The primary end-point of this study was the composite rate of major adverse cardiac or cerebrovascular events (MACCE) at 5 years, which included all-cause death, stroke, myocardial infarction (MI) and repeat revascularization. Secondary end-points consisted of the composite safety end-point of all-cause death, stroke and MI as well as the individual component of repeat revascularization. Specific definitions of these end-points have been reported previously (11). All end-points were adjudicated by an independent Clinical Events Committee that included a cardiac surgeon, a cardiologist and a neurologist.

Statistical analyses

Analyses were based on the intention-to-treat principle. Data are presented using descriptive statistics, as percentage, count of sample size or mean ± standard deviation. The Kruskal–Wallis test was used to compare continuous variables. Differences in discrete variables were compared by means of v^2 or Fisher's exact test, where appropriate. Time-to-event unadjusted and adjusted Kaplan–Meier estimates with log-rank testing were used to compare clinical outcomes after PCI and CABG among different countries. Hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for the primary end-point and the secondary end-points

were calculated relative to using Cox proportional hazards model. Treatment-by-country interactions were explored using chi-squared test. Outcomes were adjusted for a combination of preand intraoperative variables that were deemed clinically important and significantly different between countries or believed to be clinically relevant (Supplementary Material, Appendix). Schoenfeld residuals were used and showed no significant departure from the proportional hazards assumption. A 2-sided *P*-value of <0.05 was considered to be statistically significant. Analyses were performed using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA).

Table 1. Participating countries in the SYNTAX randomized cohort.

Country	Hospitals	PCI patients	CABG patients	Total no. of patients (%)	Completeness of follow-up (%)
Austria	2	28)	24	52 (2.9)	44/52 (84)
Belgium	4	44	47	91 (5.1)	83/91 (91)
Czech Republic	1)	20	20	40 (2.3)	40/40 (100)
Denmark	1	17	15	32 (1.8)	30/32 (93)
Finland	1	12	12	24 (1.3)	24/24 (100)
France	6	103	105	208 (11.6)	201/208 (96)
Germany	8	86	93	179 (9.9)	161/179 (89)
Hungary	3	44	39	83 (4.6)	75/83 (90)
Italy	7	101	96	197 (10.9)	187/197 (94)
Latvia	1	20	20	40 (2.3)	37/40 (92)
Netherlands	6	74	74	148 (8.2)	137/148 (92)
Norway	1)	4	4	8 (0.4)	8/8 (100)
Poland	3	33	33	66 (3.7)	62/66 (93)
Portugal	1	6	7	13 (0.7)	12/13 (92)
Spain	4	27	26	53 (2.9)	48/53 (90)
Sweden	3	26	28	54 (3.0)	52/54 (96)
United Kingdom	8	135	132	267 (14.8)	255/267 (95)
United States	22	123	122	245 (13.6)	220/245 (89)
TOTAL	82	903	897	1800 (100.0)	1676/1800 (93)

Values are present as N (%) or n/N (%).
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 2. Baseline characteristics of patients within countries.

	USA (n = 245)	UK (n = 267)	IT (n = 197)	GE (n = 179)	FR (n = 208)	NL (n = 148)	BE (n = 91)	HU (n = 83)	Other (n = 382)
Age	65.1 ± 10.3	65.4 ± 9.3	66.5 ± 9.1	66.6 ± 9.7	65.9 ± 10.7	64.6 ± 9.1	63.4 ± 10.9	59.0 ± 8.6	64.9 ± 9.1
Male	160 (65.3)	214 (80.1)	158 (80.2)	135 (75.4)	173 (83.2)	117 (79.1)	72 (79.1)	57 (68.7)	312 (81.7)
BMI	30.3 ± 6.2	27.7 ± 4.5	6.7 ± 3.6	227.9 ± 4.1	27.1 ± 4.7	28.1 ± 4.2	27.1 ± 4.0	29.5 ± 4.2	27.7 ± 4.3
Medically treated diabetes	78 (31.8)	48 (18.0)	60 (30.5)	54 (30.2)	51 (24.5)	32 (21.6)	16 (17.6)	28 (33.7)	85 (22.3)
Hypertension	208 (85.9)	187 (70.8)	157 (80.1)	161 (89.9)	140 (68.0)	95 (65.5)	53 (59.6)	79 (95.2)	269 (70.6)
Hyperlipidaemia	194 (79.5)	249 (93.6)	137 (69.5)	132 (73.7)	155 (75.2)	113 (76.9)	65 (72.2)	60 (76.9)	286 (75.7)
Carotid artery disease	28 (11.4)	8 (3.0)	31 (15.7)	22 (12.3)	14 (6.7)	5 (3.4)	5 (5.5)	8 (9.6)	27 (7.1)
Unstable angina	79 (32.2)	65 (24.3)	83 (42.1)	47 (26.3)	78 (37.5)	25 (16.9)	23 (25.3)	14 (16.9)	99 (25.9)
Previous MI	57 (23.3)	117 (44.3)	66 (33.5)	48 (28.4)	47 (22.6)	53 (36.1)	23 (25.8)	29 (34.9)	145 (38.4)
Congestive heart failure	19 (7.8)	8 (3.0)	6 (3.0)	7 (4.2)	4 (1.9)	3 (2.1)	1 (1.1)	5 (6.1)	30 (7.9)
Logistic EuroSCORE	4.5 ± 4.6	3.5 ± 2.3	4.8 ± 5.1	4.4 ± 5.8	3.9 ± 3.7	3.2 ± 3.4	3.7 ± 8.5	2.5 ± 3.0	3.3 ± 3.4
Number of lesions	3.6 ± 1.8	3.7 ± 1.6	4.4 ± 1.7	4.3 ± 1.7	3.9 ± 1.6	3.7 ± 1.3	3.9 ± 1.5	4.7 ± 1.8	4.0 ± 1.7
Left main, any	138 (56.3)	109 (40.8)	66 (33.5)	70 (39.3)	88 (42.3)	45 (30.4)	29 (31.9)	29 (34.9)	131 (34.3)
Left main + 2 vessel disease	49 (20.0)	40 (15.0)	18 (9.1)	19 (10.6)	32 (15.4)	7 (4.7)	9 (9.9)	6 (7.2)	38 (9.9)
Three-vessel disease only	107 (43.7)	158 (59.2)	131 (66.5)	108 (60.7)	120 (57.7)	103 (69.6)	62 (68.1)	54 (65.1)	251 (65.7)
SYNTAX score	25.7 ± 11.7	28.8 ± 10.3	31.4 ± 11.3	29.7 ± 10.8	30.5 ± 12.6	26.9 ± 10.7	26.9 ± 11.3	24.5 ± 11.4	29.9 ± 11.2

P < 0.001 for all comparison between groups. Values are shown as mean ± SD or n/N (%).

USA, United States of America; UK, United Kingdom; IT, Italy; GE, Germany; FR, France; NL, Netherlands; BE, Belgium; HU, Hungary; Other, Poland, Sweden, Spain, Czech Republic, Latvia, Denmark, Finland, Portugal and Norway; BMI, body mass index; MI, myocardial infarction.

Table 3. Procedural characteristics in PCI randomized cohort.

	USA (n = 123)	UK (n = 135)	IT (n = 101)	GE (n = 86)	FR (n = 103)	NL (n = 74)	BE (n = 44)	HU (n = 44)	Other (n = 193)
Procedure duration	90.1±42.7	98.1±33.3	123.7±47.1	89.1±40.9	87.6±40.7	106.4±58.2	88.5±31.1	95.9±36.6	121.2±50.8
Total overlapping stent	0.5±0.6	0.9±0.6	0.7±0.6	0.6±0.6	0.4±0.6	0.7±0.7	0.4±0.5	0.9±0.8	0.5±0.6
Bi-/trifurcation lesions treated	63(51.2)	87(64.4)	63(62.4)	57(66.3)	78(75.7)	45(60.8)	36(81.8)	34(77.3)	140(72.5)
Left anterior descending artery stent treated	62(50.4)	100(74.1)	50(49.5)	58(67.4)	62(60.2)	37(50.0)	20(45.5)	32(72.7)	103(53.4)
Stents implanted	4.0±2.3	4.4±1.9	5.1±2.2	5.1±2.3	4.2±2.1	4.9±2.4	4.2±1.9	6.1±2.6	4.7±2.3
Total length implanted	69.0±45.1	83.8±41.5	101.6±49.3	89.0±44.9	75.3±41.4	96.7±55.7	83.0±42.9	124.1±60.9	84.4±45.9
Long stenting (>100 mm)	25(21.2)	43(23.0)	46(45.5)	30(35.3)	23(22.8)	29(42.6)	12(28.6)	24(58.5)	62(33.0)
SYNTAX score	24.9±11.4	28.7±10.2	29.7±11.8	29.7±11.6	30.4±13.2	27.4±10.4	26.3±10.7	22.3±10.6	30.3±10.9
LogisticEuroSCORE	4.5±4.6	3.8±3.5	4.2±4.7	4.1±4.0	4.0±3.8	3.3±3.7	4.4±12.0	3.1±3.9	3.0±2.5

$P < 0.001$ for all comparison between groups. Abbreviations as in Table 2. Values are shown as mean ± SD or *n/N* (%).

RESULTS

Baseline characteristics

Of the 1800 patients enrolled in the SYNTAX trial, complete follow-up data were obtained for 1676 patients (93.1%). Completeness of follow-up was comparable between groups of countries ($P = 0.084$) (Table 1). The risk profile of patients varied significantly among countries (Table 2, complete results are in Supplementary Material, Table S1). Patients in Hungary were the youngest, had the highest number of patients with medically treated hypertension and medically treated diabetes, while perioperative risk expressed by the logistic EuroSCORE was the lowest. In contrast, patients from the USA and Italy were at greater operative risk according to the logistic EuroSCORE. Patients in the UK had the highest rates of prior MI and therefore more frequent pretreatment left ventricular dysfunction. The SYNTAX score was substantially lower in Hungary, while more patients in the USA had LM disease (Table 2).

Procedural characteristics

Several differences were noted in PCI characteristics (Table 3, complete results are in Supplementary Material, Table S2). Particularly in Hungary a larger number of stents were implanted, a higher stent length, and more patients had >100mm stents. There were no significant differences in the rates of complete revascularization. Patients in the USA received the lowest total length of implanted stents. Remarkably, patients in Germany more often underwent staged procedures compared with patients in Italy and France.

Table 4. Procedural characteristics in CABG randomized cohort.

	USA (n=122)	UK (n = 132)	IT (n = 96)	GE (n=93)	FR (n=105)	NL (n=74)	BE (n=47)	HU (n = 39)	Other (n = 189)
Elective procedure	104 (89.7)	124 (96.9)	87 (94.6)	88 (87.8)	89 (89.0)	68 (97.1)	42 (93.3)	20 (62.5)	166 (91.7)
Procedure time	235.9 ± 72.2	181.5 ± 58.3	230.0±51.7	236.4 ± 71.6	207.4 ±48.1	190.5 ± 59.8	198.1±49.8	183.3 ± 51.6	203.1 ± 57.8
Bypass time	103.6 ± 41.5	72.2 ± 31.6	86.2 ± 26.4	93.9 ± 39.9	88.2±37.1	84.3 ± 35.9	79.6 ± 25.6	78.0 ± 22.1	87.4 ± 33.8
Cross-clamp time	75.2 ± 34.7	49.3 ± 66.3	57.7 ± 16.6	59.9 ± 25.7	61.5±23.7	51.9 ± 21.2	42.5 ± 19.1	45.2 ± 14.4	50.1 ± 21.8
Blood cardioplegia	75 (64.7)	78 (60.9)	55 (60.4)	38 (42.2)	89 (89.0)	18 (25.7)	2 (4.4)	1 (3.1)	71 (39.2)
Complete revascularization	87 (75.0)	87 (68.0)	49 (53.3)	68 (75.6)	46 (46.0)	54 (77.1)	34 (75.6)	10 (31.3)	110 (60.8)
Off-pump surgery	37 (31.9)	5 (3.9)	10 (10.9)	17 (18.9)	4 (4.0)	2 (2.9)	20 (44.4)	3 (9.4)	30 (16.6)
Grafts per patient	3.0 ± 0.7	2.9±0.8	2.8±0.7	2.7±0.6	2.7 ± 0.6	2.2±0.5	2.9±0.7	3.1±0.8	2.7 ± 0.7
Arterial	1.2 ± 0.5	1.2±0.5	1.4±0.5	1.7±0.7	1.9 ± 0.8	1.2±0.6	1.7±0.6	0.9±0.6	1.3 ± 0.6
Distal anastomoses	3.3 ± 0.9	3.0±0.7	3.1±0.9	3.2±0.9	2.9 ± 0.8	3.7±1.0	3.4±1.0	3.2±0.8	3.2 ± 0.9
LIMA use	114 (98.3)	123 (96.1)	91 (98.9)	89 (98.8)	97 (97.0)	64 (91.4)	44 (97.8)	26 (83.9)	179 (98.9)
Double LIMA/RIMA	15 (13.0)	10 (7.8)	29 (32.2)	39 (43.3)	60 (60.6)	18 (25.7)	30 (68.2)	4 (12.5)	31 (17.5)
Radial artery use	9 (7.8)	15 (11.7)	5 (5.4)	21 (23.3)	29 (29.0)	3 (4.3)	3 (6.7)	0	35 (19.3)
Complete arterial revascularization	8 (6.9)	10 (7.8)	9 (9.8)	33 (36.7)	48 (48.0)	8 (11.4)	6 (13.3)	2 (6.3)	37 (20.4)
SYNTAX score	26.5 ± 12.0	29.0 ± 10.3	33.3 ± 10.4	29.8 ± 10.2	30.5±12.1	26.3 ± 11.0	27.4 ± 11.9	27.0 ± 11.9	29.5 ± 11.6
Logistic EuroSCORE	4.4 ± 4.6	3.3±3.1	5.5±5.4	4.8±7.1	3.7 ± 3.7	3.2±3.0	3.0±2.7	1.9±1.5	3.6 ± 4.0

P< 0.001 for all comparison between groups. Abbreviations as in Table 2. Values are shown as mean ± SD or *n*/*N* (%). LIMA, left internal mammary artery; RIMA, right internal mammary artery.

Differences in CABG procedural characteristics are listed in Table 4 and Fig. 1 (complete results are in Supplementary Material, Table S3). First of all, the necessity for emergent treatment was significantly higher in Hungary compared with the other groups. Secondly, the procedure, bypass and cross-clamp times showed significant variations. Thirdly, in the Netherlands, less grafts were used than in other countries, but the number of distal anastomoses was the highest, indicating that more jump grafts were used compared with other countries. When comparing type of conduits, the use of an arterial graft to the left anterior descending artery, as well as the rate of complete arterial grafting, were lowest in Hungary. In France, the use of arterial grafts was highest, resulting in the highest rate of complete arterial grafting. In Belgium, the rate of bilateral internal mammary artery (IMA) use was highest, but the rate of complete arterial grafting was lower because of the use of additional venous grafts.

Medication at discharge

There were only marginal differences across groups in prescribing antiplatelet treatment after PCI; the prescription of thienopyridine and dual antiplatelet therapy was lowest in the Netherlands. There were, however, significant differences in the prescription of statins, beta-blockers and antihypertensive medication (Supplementary Material, Table S4).

After CABG, there were differences in the prescription of all secondary prevention medications (Supplementary Material, Table S4). In the Netherlands and Germany, the prescription of antiplatelet therapy was lowest, but the prescription of Coumadin derivates was higher. Thienopyridines were prescribed at the highest rate in the USA, as was the prescription of dual antiplatelet therapy.

Five-year outcomes

For the entire cohort, the 5-year unadjusted Kaplan–Meier estimates of MACCE were lowest in the group of other countries (28.0%) and highest in Germany (39.4%, log-rank for all groups $P = 0.076$) (Fig. 2A). Also, the unadjusted rate of the composite safety end-point of death/stroke/MI was highest in Germany (26.4%) but lowest in Hungary (12.9%) (log-rank for all groups $P = 0.096$) (Fig. 2B). Repeat revascularization was lowest in the UK (14.1%) and highest in Hungary (31.6%), with significant differences across groups ($P = 0.008$) (Fig. 2C).

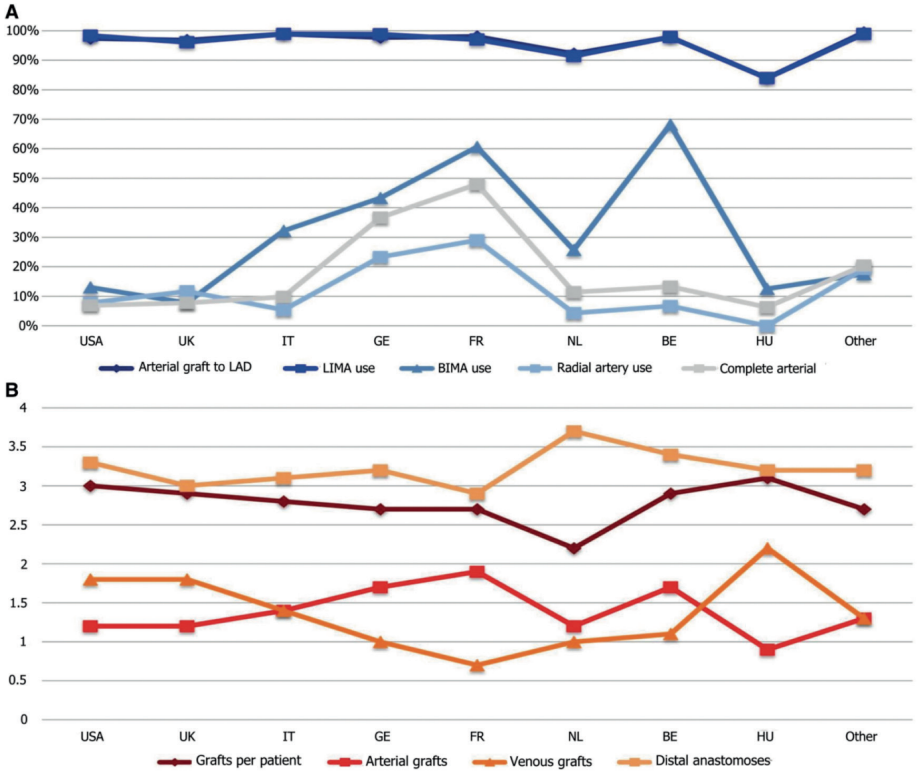


Figure 1. A graphical display showing differences among investigating countries in use percentage of arterial conduits **(A)** and a number of implanted grafts **(B)**. USA, United States of America; UK, United Kingdom; IT, Italy; GE, Germany; FR, France; NL, Netherlands; BE, Belgium; HU, Hungary; Other, Poland, Sweden, Spain, Czech Republic, Latvia, Denmark, Finland, Portugal and Norway; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; LAD, left anterior descending artery.

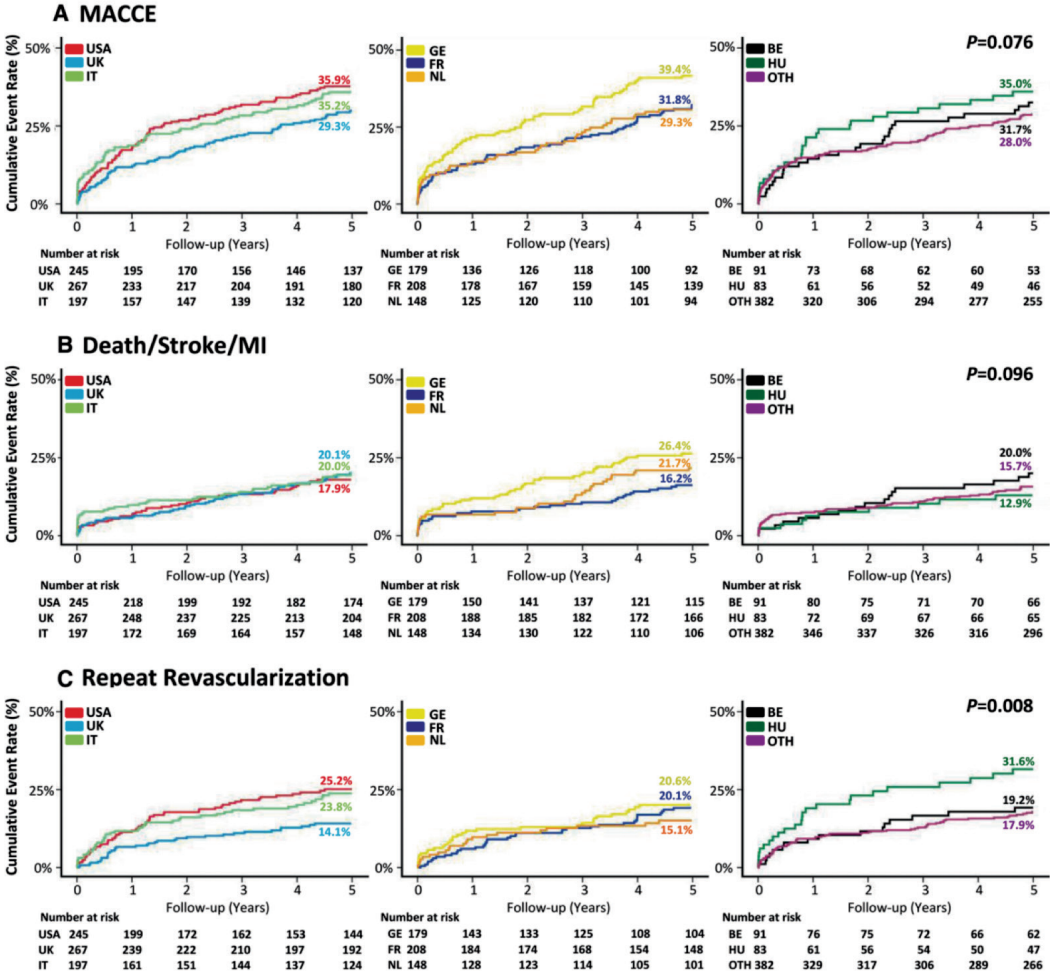


Figure 2. The Kaplan–Meier cumulative event curves by investigating countries in the SYNTAX trial for MACCE **(A)**, the composite safety end-point of death/stroke/MI **(B)** and repeat revascularization **(C)**. Abbreviations as in Fig. 1. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

After PCI, patients in France had the lowest unadjusted event rates of MACCE (28.9%), the composite safety end-point of death/stroke/MI (13.7%) and rate of repeat revascularization (20.3%), while these rates were highest in Hungary (50.4, 18.2 and 44.9%, respectively) and Germany (46.8, 29.2 and 29%, respectively; Fig. 3A and C). After adjustment for baseline and procedural characteristics and with the USA as reference, patients in France had a lower risk of MACCE (HR = 0.60, 95% CI 0.37–0.98) and for the composite safety end-point of death/stroke/MI (HR = 0.45, 95% CI 0.22–0.89), while patients enrolled in Hungary had a higher risk of repeat revascularization (HR = 1.89, 95% CI 1.14–3.42) (Supplementary Material, Table S5).

After CABG, rates of unadjusted MACCE were lowest in Hungary and highest in France (15.3% vs 34.6%), with significant differences among the 9 groups studied (log-rank for all; *P* = 0.026; Fig. 3B). Differences in the unadjusted rates of repeat revascularization just failed to reach statistical significance (*P* = 0.07; Fig. 3D and F). After adjustment for baseline and procedural characteristics and with the USA as reference, patients enrolled in Germany had a higher adjusted risk for the composite of death/stroke/MI (HR = 2.38, 95% CI 1.03–5.67), and in the UK, patients had a lower adjusted risk of repeated revascularization (HR = 0.32, 95% CI 0.12– 0.85; Supplementary Material, Table S5).

The PCI versus CABG treatment effect did not show a significant interaction among countries for the end-point of MACCE (Fig. 4A) or the composite safety end-point of death/stroke/MI (Fig. 4B). For repeat revascularization, there was a significant treatment-bycountries interaction (*P* for interaction = 0.045) (Fig. 4C).

DISCUSSION

This study demonstrates important differences in the baseline characteristics, clinical practice, medication regimens and outcomes among patients undergoing revascularization in the different countries involved in the SYNTAX trial. Comorbidities and hence the logistic EuroSCORE differed between countries, there was a major variation in the complexity of coronary disease according to SYNTAX score, and there was a significant difference in 5-year outcomes between countries.

Geographical variations in patient characteristics and the impact on outcome have recently been reported in cardiovascular trials like the EVEREST and ASTRONAUT trial (4, 13–15). The current analysis is unique, as for the first time, it estimates the impact of the difference in patient characteristics and clinical practice on outcomes after PCI and CABG in specific countries. The number of patients with clinically relevant comorbidities was highest in the USA and Italy, while patients from countries with lower enrolment (Hungary and the pooled group of other (small) countries) had less comorbidities. In concordance with other studies, countries with low recruiting centres tended to enrol lower risk patients (5).

PCI-treated patients in Hungary were the youngest and had the lowest SYNTAX score, while the number of implanted stents was higher, less optimal use of secondary prevention medication and they experienced significantly more repeated revascularizations. These findings may therefore confirm the importance of functional assessment of coronary lesions as opposed to anatomical assessment and the use of secondary prevention. Despite recommendations provided in the SYNTAX trial protocols, differences in prescription of secondary prevention medications are notable and could have had a negative impact on the outcome. Lack of optimal therapy and correlation with long-term mortality has been reported in previous studies (16, 17). Antiplatelet agents and statins were more often used after PCI than after CABG. Preventive medications to maintain stent patency after PCI were rigorously prescribed by cardiologists, whereas usefulness of secondary prevention was probably underestimated after CABG (18). These findings provide an opportunity for quality improvement in discharge medication after CABG in several countries but also remind and encourage cardiologists, intensivists and cardiac surgeons to start with secondary prevention as soon as possible and to discharge patients with optimal therapies, since there is a possibility that primary care doctors who will follow-up these patients will not initiate treatment.

Substantial differences were noted in surgical techniques across countries. Despite clear recommendations of more arterial grafting in guidelines (19, 20), the published rates of arterial grafting are still relatively low (21). Differences in the use of the left and/or right IMAs, total arterial revascularization, the number of grafts, myocardial protection and the use of off-pump procedures are likely to be influenced by surgical training rather than the risk profile of the patient. It is remarkable that a procedure that is performed with such a high rate since its introduction more than 50 years ago remains far away from being standardized globally. Despite evidence of a survival benefit in favour of the use of 2 IMAs over the use of a single IMA graft (22), their use in the USA, the UK and Hungary was disappointingly low. On the other

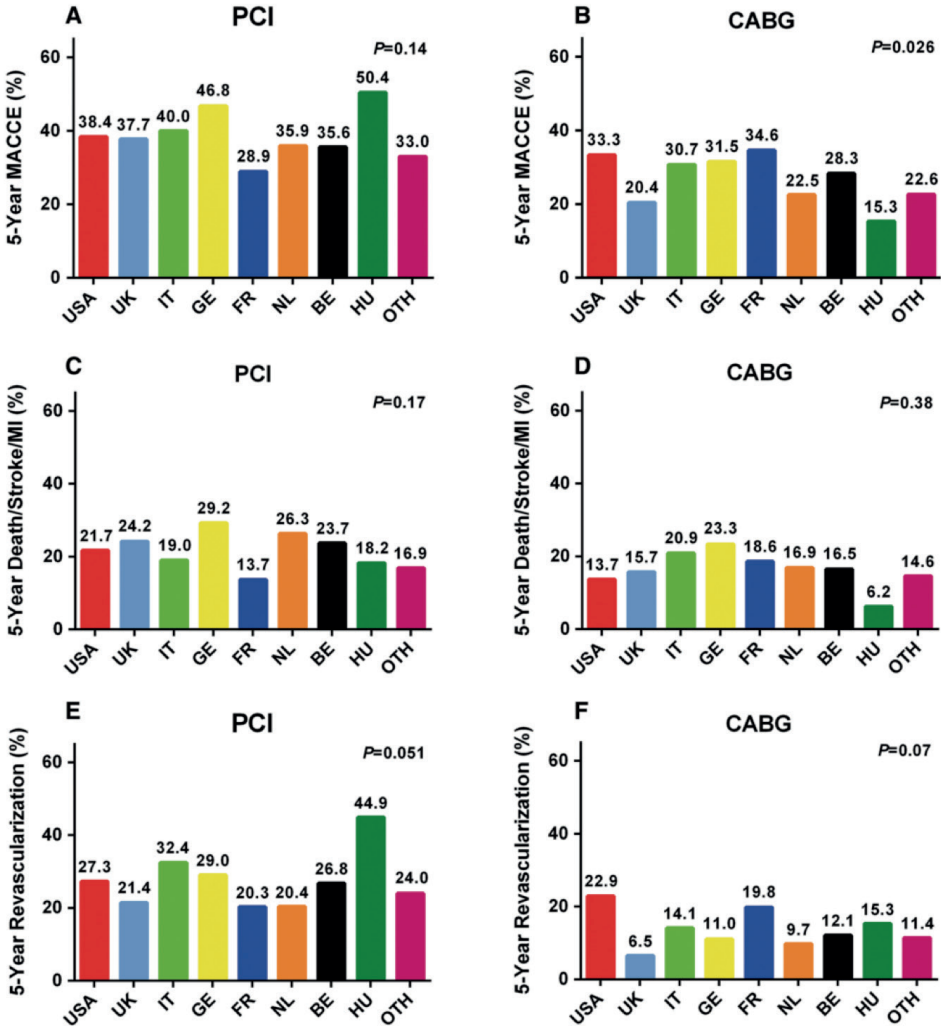


Figure 3. A graphical display of 5-year outcomes of CABG and PCI cohorts by investigating countries in the SYNTAX trial for MACCE **(A and B)**, the composite safety end-point of death/stroke/MI **(C and D)** and repeat revascularization **(E and F)**. Abbreviations as in Fig. 1. Values are Kaplan–Meier rates with *P*-values from log-rank test.

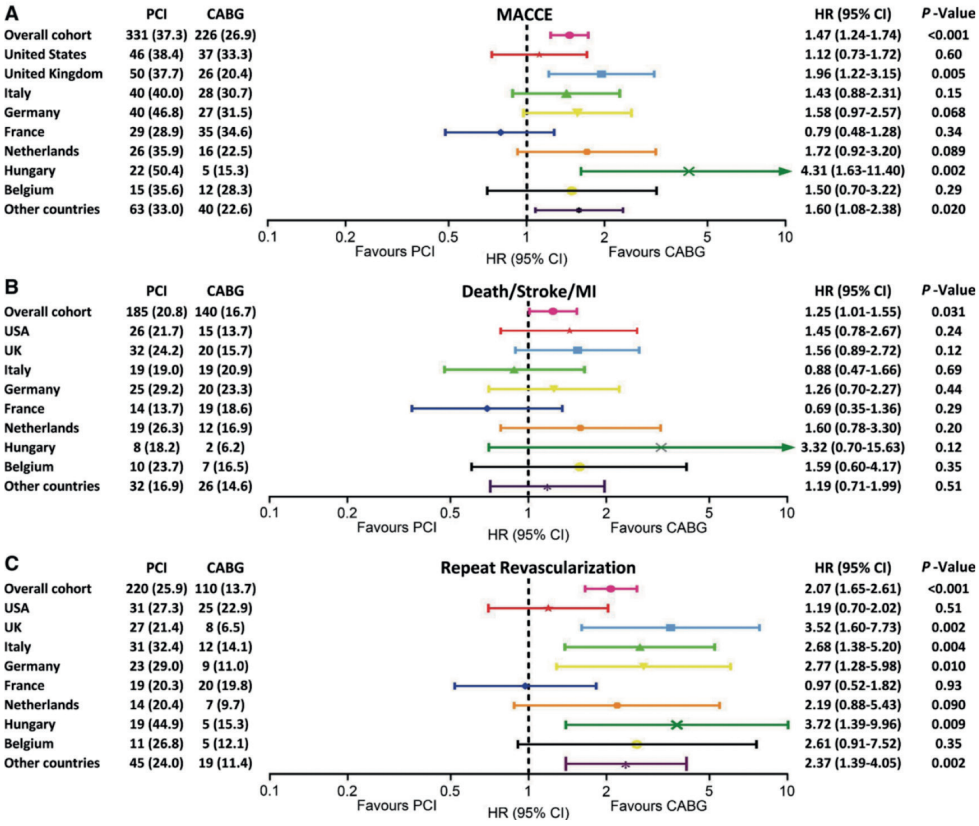


Figure 4. A graphical display of 5-year outcomes between investigating countries for MACCE **(A)**, the composite safety end-point of death/stroke/MI **(B)** and repeat revascularization **(C)**. Treatment-by-country interaction failed to reach statistical significance for MACCE (P_{int} = 0.12) and the composite safety end-point (P_{int} = 0.38), but there is significant interaction for repeat revascularization (P_{int} = 0.045). Abbreviations as in Fig. 1. Values are Kaplan–Meier rates with *P*-values from log-rank test. HR, hazard ratio.

hand, in the majority of the patients who underwent CABG in Belgium and France, 2 IMAs graft were used. In this regard, it is important to consider the absence of a midterm benefit on clinical outcomes from 2 IMAs over single IMA graft in the recent 5-year findings from the Arterial Revascularization Trial (23), although the benefits of 2 IMA grafts increase with the duration of follow-up, which formed the basis for the current Arterial Revascularization Trial with 10-year follow-up.

After adjustment for baseline clinical patterns, PCI-treated patients in France had a significantly lower MACCE rate and CABG patients in Germany had a higher incidence of the composite of death, stroke and MI. It remains unclear whether any unmeasured confounding may play a role or whether these findings indeed represent higher risks of adverse events in specific countries. Furthermore, a large difference in repeat revascularization among countries persisted, even after adjustment. It is notable that the Netherlands and the UK cohorts had the lowest rates of repeated revascularization, whereas other countries (USA, Hungary and Italy) had a higher incidence of repeat revascularization (24).

In order to reduce the difference in outcome between different institutions and countries, future trials should include standardized protocols for techniques and treatment strategies. Rigorous training and monitoring to improve adherence to these protocols will be key to improving the quality of a trial. Moreover, the design of the SYNTAX trial did not ensure balanced allocation within participating countries, which may have had an impact on trial outcomes. Stratifying enrolment per country will strengthen the external validation of trial results.

Study limitations

Since the SYNTAX trial was designed to test the difference between PCI and CABG and not differences among countries, this *post hoc* analysis should be interpreted as hypothesis generating. However, exploration of clinical patterns by countries provides a better insight of the trial in order to investigate a possible geographical heterogeneity (1). These analyses were restricted to specific countries based on the number of included patients and adverse events during 5-year of follow-up. Pooling data from countries with few participants into 1 group might be somewhat arbitrary and heterogeneity within this subgroup is likely (1). Unmeasured factors such as the medical care delivery system, disease awareness on a population-based scale and patient culture might also play an important role beyond clinical and procedural characteristics (25). In addition, another bias might be a lower threshold for repeat revascularization that may influence the results (15, 26).

CONCLUSIONS

Baseline characteristics, clinical practice, secondary prevention medication regimens and outcomes were different across countries in the SYNTAX trial. These data can be used to improve treatment strategies to reduce adverse events after myocardial revascularization in specific countries. It points to the fact that, in strategy trials like SYNTAX, the results are relevant to a definable group of patients in a particular clinical setting. Standardization of treatment strategies may help to improve the external validity of trial results and improve recommendation in guidelines.

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SUPPLEMENTAL MATERIAL

Appendix 1. Baseline variables included in univariate analyses to predict MACCE, the composite safety endpoint of death/stroke/myocardial infarction and repeat revascularization.

In the Cox proportional model, the following variables were added: male gender, age, body mass index, medically treated diabetes, peripheral vascular disease, creatinine blood level > 200 micromol/L, medically treated hypertension, medically treated hyperlipidemia, carotid artery disease, unstable angina, prior myocardial infarction, congestive heart failure, pulmonary hypertension, moderate left ventricular ejection fraction 30-49%, left main disease, number of lesion (determined by Core lab), SYNTAX score, PCI versus CABG, incomplete revascularization, enrolment in the United States of America, enrolment in the United Kingdom, enrolment in Italy, enrolment in Germany, enrolment in France, enrolment in the Netherlands, enrolment in Belgium, enrolment in Hungary and enrolment in group of other countries (Austria, Poland, Sweden, Latvia, Denmark, Czech Republic, Finland, Spain, Portugal and Norway).

Additional variables added in the separate PCI model: number of stents implanted, total stent length implanted, staged procedure, LAD treated, the number of overlapping stents and bi/trifurcation treated. The variable 'PCI versus CABG treatment' was deleted in this model.

Additional variables added in the separate CABG model: procedure time, bypass time, off-pump procedure, left internal mammary artery use, bilateral internal mammary artery use, complete arterial revascularization, the number of grafts and number of distal anastomoses. The variable 'PCI versus CABG treatment' was deleted in this model.

Supplemental Table 1. Baseline characteristics of patients within countries.

	USA (245)	UK (267)	IT (197)	GE (179)	FR (208)	NL (148)	BE (91)	HU (83)	Other (382)	P-Value
Age	65.1±10.3	65.4±9.3	66.5±9.1	66.6±9.7	65.9±10.7	64.6±9.1	63.4±10.9	59.0±8.6	64.9±9.1	<0.001
Male	160 (65.3)	214 (80.1)	158 (80.2)	135 (75.4)	173 (83.2)	117 (79.1)	72 (79.1)	57 (68.7)	312 (81.7)	<0.001
BMI	30.3±6.2	27.7±4.5	26.7±3.6	27.9±4.1	27.1±4.7	28.1±4.2	27.1±4.0	29.5±4.2	27.7±4.3	<0.001
Current smoker	58 (24.6)	46 (17.4)	32 (16.9)	29 (16.7)	42 (20.4)	32 (22.4)	21 (23.1)	17 (20.7)	86 (23.0)	0.33
Medical Treated Diabetes	78 (31.8)	48 (18.0)	60 (30.5)	54 (30.2)	51 (24.5)	32 (21.6)	16 (17.6)	28 (33.7)	85 (22.3)	<0.001
Insulin requiring	34 (13.9)	21 (7.9)	25 (12.7)	21 (11.7)	16 (7.7)	16 (10.8)	5 (5.5)	11 (13.3)	33 (8.6)	0.125
Peripheral vascular disease	32 (13.1)	15 (5.6)	23 (11.7)	15 (8.4)	27 (13.0)	14 (9.5)	6 (6.6)	6 (7.2)	39 (10.2)	0.095
COPD	25 (10.2)	20 (7.5)	19 (9.6)	12 (6.7)	12 (5.8)	19 (12.8)	7 (7.7)	5 (6.0)	35 (9.2)	0.36
Creatinine >200 µmol/l	7 (2.9)	1 (0.4)	4 (2.0)	5 (2.8)	0	0	0	1 (1.2)	8 (2.1)	0.041
Hypertension	208 (85.9)	187 (70.8)	157 (80.1)	161 (89.9)	140 (68.0)	95 (65.5)	53 (59.6)	79 (95.2)	269 (70.6)	<0.001
Hyperlipidemia	194 (79.5)	249 (93.6)	137 (69.5)	132 (73.7)	155 (75.2)	113 (76.9)	65 (72.2)	60 (76.9)	286 (75.7)	<0.001
Carotid artery disease	28 (11.4)	8 (3.0)	31 (15.7)	22 (12.3)	14 (6.7)	5 (3.4)	5 (5.5)	8 (9.6)	27 (7.1)	<0.001
History of CVA or TIA	29 (12.0)	23 (8.6)	19 (9.7)	8 (4.5)	14 (6.7)	13 (8.8)	4 (4.4)	8 (9.8)	32 (8.5)	0.21
Unstable angina	79 (32.2)	65 (24.3)	83 (42.1)	47 (26.3)	78 (37.5)	25 (16.9)	23 (25.3)	14 (16.9)	99 (25.9)	<0.001
Previous MI	57 (23.3)	117 (44.3)	66 (33.5)	48 (28.4)	47 (22.6)	53 (36.1)	23 (25.8)	29 (34.9)	145 (38.4)	<0.001
Congestive heart failure	19 (7.8)	8 (3.0)	6 (3.0)	7 (4.2)	4 (1.9)	3 (2.1)	1 (1.1)	5 (6.1)	30 (7.9)	<0.001
Pulmonary hypertension	4 (1.6)	1 (0.4)	6 (3.0)	2 (1.1)	0	3 (2.0)	1 (1.1)	0	3 (0.8)	0.099
LVEF poor (<30%)	5 (2.0)	7 (2.6)	6 (3.0)	7 (3.9)	1 (0.5)	3 (2.0)	0	1 (1.2)	4 (1.0)	0.16
LVEF moderate (30-49%)	43 (17.6)	60 (22.5)	38 (19.3)	33 (18.4)	26 (12.5)	29 (19.6)	6 (6.6)	17 (20.5)	61 (16.0)	0.022
Logistic EuroSCORE	4.5±4.6	3.5±2.3	4.8±5.1	4.4±5.8	3.9±3.7	3.2±3.4	3.7±8.5	2.5±3.0	3.3±3.4	<0.001
Number of lesion	3.6±1.8	3.7±1.6	4.4±1.7	4.3±1.7	3.9±1.6	3.7±1.3	3.9±1.5	4.7±1.8	4.0±1.7	<0.001
Left main, any	138 (56.3)	109 (40.8)	66 (33.5)	70 (39.3)	88 (42.3)	45 (30.4)	29 (31.9)	29 (34.9)	131 (34.3)	<0.001
LM+ 1 vessel	28 (11.4)	24 (9.0)	10 (5.1)	15 (8.4)	12 (5.8)	11 (7.4)	6 (6.6)	2 (2.4)	30 (7.9)	0.15
LM+ 2 vessel	49 (20.0)	40 (15.0)	18 (9.1)	19 (10.6)	32 (15.4)	7 (4.7)	9 (9.9)	6 (7.2)	38 (9.9)	<0.001
LM+ 3 vessel	37 (15.1)	33 (12.4)	32 (16.2)	28 (15.6)	37 (17.8)	21 (14.2)	11 (12.1)	20 (24.1)	39 (10.2)	0.043
Three-vessel disease only	107 (43.7)	158 (59.2)	131 (66.5)	108 (60.7)	120 (57.7)	103 (69.6)	62 (68.1)	54 (65.1)	251 (65.7)	<0.001
Total occlusion	46 (19.0)	58 (22.0)	48 (24.4)	44 (24.9)	57 (27.5)	34 (23.1)	20 (22.0)	20 (24.4)	88 (23.2)	0.72
Bifurcation, any	156 (64.5)	192 (72.7)	149 (75.6)	135 (76.3)	153 (73.9)	105 (71.4)	59 (64.8)	53 (64.6)	298 (78.4)	0.004
Trifurcation, any	15 (6.2)	33 (12.5)	24 (12.2)	21 (11.9)	23 (11.1)	11 (7.5)	6 (6.6)	7 (8.5)	50 (13.2)	0.12
SYNTAX score	25.7±11.7	28.8±10.3	31.4±11.3	29.7±10.8	30.5±12.6	26.9±10.7	26.9±11.3	24.5±11.4	29.9±11.2	<0.001

USA, The United States of America; UK, The United Kingdom; IT, Italy; GE. Germany; FR, France; NL, The Netherlands; BE, Belgium; HU, Hungary; Other, Poland and Sweden and Spain and Czech Republic and Latvia and Denmark and Finland and Portugal and Norway. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transit ischemic attack, MI, myocardial infarction; LVEF, left ventricular ejection fraction. Values are shown as mean ± SD or n/N (%).

Supplemental Table 2. Procedural characteristics in PCI randomized cohort.

	USA (n=123)	UK (n=135)	IT (n=101)	GE (n=86)	FR (n=103)	NL (n=74)	BE (n=44)	HU (n=44)	Other (n=193)	P-Value
Revascularization presentation										
Urgent	9 (7.6)	3 (2.2)	9 (8.9)	5 (5.8)	2 (2.0)	1 (1.4)	1 (2.4)	1 (2.3)	5 (2.6)	0.047
Emergent	1 (0.8)	3 (2.2)	0	1 (1.2)	5 (5.0)	0	0	0	6 (3.1)	0.10
Elective	109 (91.6)	128 (95.6)	92 (91.1)	80 (93.0)	94 (93.0)	68 (98.6)	41 (97.6)	43 (97.7)	180 (94.3)	0.40
Procedure duration	90.1±42.7	98.1±33.3	123.7±47.1	89.1±40.9	87.6±40.7	106.4±58.2	88.5±31.1	95.9±36.6	121.2±50.8	<0.001
Complete revascularization	76 (63.9)	73 (54.5)	59 (58.4)	48 (55.8)	54 (53.5)	43 (62.3)	22 (52.4)	20 (45.5)	102 (53.4)	0.49
Total overlapping stent	0.5±0.6	0.9±0.6	0.7±0.6	0.6±0.6	0.4±0.6	0.7±0.7	0.4±0.5	0.9±0.8	0.5±0.6	<0.001
Staged procedure	19 (16.0)	16 (11.9)	9 (8.9)	24 (27.9)	7 (6.9)	12 (17.4)	5 (11.9)	5 (11.4)	28 (14.7)	0.005
Bi/trifurcation lesion treated	63 (51.2)	87 (64.4)	63 (62.4)	57 (66.3)	78 (75.7)	45 (60.8)	36 (81.8)	34 (77.3)	140 (72.5)	<0.001
LAD stent treated	62 (50.4)	100 (74.1)	50 (49.5)	58 (67.4)	62 (60.2)	37 (50.0)	20 (45.5)	32 (72.7)	103 (53.4)	<0.001
Stents implanted	4.0±2.3	4.4±1.9	5.1±2.2	5.1±2.3	4.2±2.1	4.9±2.4	4.2±1.9	6.1±2.6	4.7±2.3	<0.001
Total length implanted	69.0±45.1	83.8±41.5	101.6±49.3	89.0±44.9	75.3±41.4	96.7±55.7	83.0±42.9	124.1±60.9	84.4±45.9	<0.001
Long stenting (>100mm)	25 (21.2)	43 (23.0)	46 (45.5)	30 (35.3)	23 (22.8)	29 (42.6)	12 (28.6)	24 (58.5)	62 (33.0)	<0.001
SYNTAX score	24.9±11.4	28.7±10.2	29.7±11.8	29.7±11.6	30.4±13.2	27.4±10.4	26.3±10.7	22.3±10.6	30.3±10.9	<0.001
Logistic EuroSCORE	4.5±4.6	3.8±3.5	4.2±4.7	4.1±4.0	4.0±3.8	3.3±3.7	4.4±12.0	3.1±3.9	3.0±2.5	<0.001

Abbreviations as in supplemental Table 1. LAD, left anterior descending artery. Values are shown as mean ± SD or n/N (%).

Supplemental Table 3. Procedural characteristics in CABG randomized cohort.

	USA (n=122)	UK (n=132)	IT (n=96)	GE (n=93)	FR (n=105)	NL (n=74)	BE (n=47)	HU (n=39)	Other (n=189)	P-Value
Revascularization presentation										
Urgent	10 (8.6)	3 (2.3)	4 (4.3)	1 (1.1)	2 (2.0)	1 (1.4)	2 (4.4)	1 (3.1)	9 (5.0)	<0.001
Emergent	2 (1.7)	1 (0.8)	1 (1.1)	1 (1.1)	9 (9.0)	1 (1.4)	1 (2.2)	11 (34.4)	6 (3.3)	<0.001
Elective	104 (89.7)	124 (96.9)	87 (94.6)	88 (87.8)	89 (89.0)	68 (97.1)	42 (93.3)	20 (62.5)	166 (91.7)	<0.001
Procedure time	235.9±72.2	181.5±58.3	230.0±51.7	236.4±71.6	207.4±48.1	190.5±59.8	198.1±49.8	183.3±51.6	203.1±57.8	<0.001
Bypass time	103.6±41.5	72.2±31.6	86.2±26.4	93.9±39.9	88.2±37.1	84.3±35.9	79.6±25.6	78.0±22.1	87.4±33.8	<0.001
Cross-clamp time	75.2±34.7	49.3±66.3	57.7±16.6	59.9±25.7	61.5±23.7	51.9±21.2	42.5±19.1	45.2±14.4	50.1±21.8	<0.001
Cardioplegia										
Crystalloid	8 (6.9)	43 (33.6)	21 (22.8)	30 (33.3)	1 (1.0)	49 (70.0)	17 (37.8)	28 (87.5)	81 (44.8)	<0.001
Blood	75 (64.7)	78 (60.9)	55 (60.4)	38 (42.2)	89 (89.0)	18 (25.7)	2 (4.4)	1 (3.1)	71 (39.2)	<0.001
Complete revascularization	87 (75.0)	87 (68.0)	49 (53.3)	68 (75.6)	46 (46.0)	54 (77.1)	34 (75.6)	10 (31.3)	110 (60.8)	<0.001
Off-pump surgery	37 (31.9)	5 (3.9)	10 (10.9)	17 (18.9)	4 (4.0)	2 (2.9)	20 (44.4)	3 (9.4)	30 (16.6)	<0.001
Grafts per patient	3.0±0.7	2.9±0.8	2.8±0.7	2.7±0.6	2.7±0.6	2.2±0.5	2.9±0.7	3.1±0.8	2.7±0.7	<0.001
Arterial	1.2±0.5	1.2±0.5	1.4±0.5	1.7±0.7	1.9±0.8	1.2±0.6	1.7±0.6	0.9±0.6	1.3±0.6	<0.001
Venous	1.8±0.8	1.8±0.9	1.4±0.7	1.0±0.9	0.7±0.8	1.0±0.5	1.1±0.7	2.2±0.9	1.3±0.9	<0.001
Distal anastomoses	3.3±0.9	3.0±0.7	3.1±0.9	3.2±0.9	2.9±0.8	3.7±1.0	3.4±1.0	3.2±0.8	3.2±0.9	<0.001
Arterial graft to LAD	113 (97.4)	121 (96.8)	91 (98.9)	86 (97.7)	97 (98.0)	59 (92.2)	44 (97.8)	26 (83.9)	179 (99.4)	0.018
LIMA use	114 (98.3)	123 (96.1)	91 (98.9)	89 (98.8)	97 (97.0)	64 (91.4)	44 (97.8)	26 (83.9)	179 (98.9)	<0.001
Double LIMA/RIMA	15 (13.0)	10 (7.8)	29 (32.2)	39 (43.3)	60 (60.6)	18 (25.7)	30 (68.2)	4 (12.5)	31 (17.5)	<0.001
Radial artery use	9 (7.8)	15 (11.7)	5 (5.4)	21 (23.3)	29 (29.0)	3 (4.3)	3 (6.7)	0	35 (19.3)	<0.001
Complete arterial revascularization	8 (6.9)	10 (7.8)	9 (9.8)	33 (36.7)	48 (48.0)	8 (11.4)	6 (13.3)	2 (6.3)	37 (20.4)	<0.001
SYNTAX score	26.5±12.0	29.0±10.3	33.3±10.4	29.8±10.2	30.5±12.1	26.3±11.0	27.4±11.9	27.0±11.9	29.5±11.6	<0.001
Logistic EuroSCORE	4.4±4.6	3.3±3.1	5.5±5.4	4.8±7.1	3.7±3.7	3.2±3.0	3.0±2.7	1.9±1.5	3.6±4.0	<0.001

Abbreviations as in supplemental Table 1. LAD, left anterior descending artery; LIMA, left internal mammary artery; RIMA, right internal mammary artery. Values are shown as mean ± SD or n/N (%).

Supplemental Table 4. Medication prescribed at discharge.

	USA (245)	UK (267)	IT (197)	GE (179)	FR (208)	NL (148)	BE (91)	HU (83)	Other (382)	P-Value
PCI group										
Acetylsalicylic Acid	118 (96.7)	133 (98.5)	95 (94.1)	83 (96.4)	98 (97.0)	68 (91.9)	40 (95.2)	43 (97.7)	185 (96.9)	0.42
Thienopyridine	119 (97.5)	133 (98.5)	98 (97.0)	85 (98.8)	100 (99.0)	67 (90.5)	42 (100.0)	40 (90.9)	183 (95.8)	0.009
Antiplatelet, Any	120 (98.4)	134 (99.3)	98 (97.0)	86 (100.0)	101 (99.0)	72 (97.3)	42 (100.0)	43 (97.7)	189 (99.0)	0.47
DAPT	117 (95.9)	132 (97.8)	95 (94.1)	82 (95.3)	97 (96.0)	64 (86.5)	40 (95.2)	40 (90.9)	181 (94.8)	0.070
Coumadin Derivatives	7 (5.7)	1 (0.7)	2 (2.0)	4 (4.7)	1 (1.0)	4 (5.4)	1 (2.4)	1 (2.3)	2 (1.0)	0.045
Statin Therapy	105 (86.1)	129 (95.6)	84 (83.2)	69 (80.2)	92 (91.1)	61 (82.4)	34 (81.0)	35 (79.5)	168 (88.0)	0.011
Beta-blockers	92 (75.4)	106 (78.5)	75 (74.3)	77 (89.5)	87 (86.1)	60 (81.1)	27 (64.3)	33 (75.0)	171 (89.5)	<0.001
ARB or ACE Inhibitors	75 (61.5)	92 (68.1)	73 (72.3)	76 (88.4)	60 (59.4)	32 (43.2)	16 (38.1)	39 (88.6)	137 (71.7)	<0.001
Calcium Channel Blockers	19 (15.6)	30 (22.2)	26 (25.7)	24 (27.9)	31 (30.7)	18 (24.3)	8 (19.0)	16 (36.4)	59 (30.9)	0.054
Amiodarone	5 (4.1)	2 (1.5)	2 (2.0)	1 (1.2)	1 (1.0)	1 (1.4)	0	1 (2.3)	0	0.26
Cardiac glycoside	3 (2.5)	1 (0.7)	1 (1.0)	1 (1.2)	0	0	0	0	0	0.31
Diuretics	32 (26.2)	32 (23.7)	18 (17.8)	44 (51.2)	13 (12.9)	14 (18.9)	6 (14.3)	18 (40.9)	35 (18.3)	<0.001
H2-receptors blockers	9 (7.4)	3 (2.2)	49 (48.5)	4 (4.7)	14 (13.9)	4 (5.4)	1 (2.4)	22 (50.0)	24 (12.6)	<0.001
CABG group										
Acetylsalicylic Acid	113 (95.0)	116 (89.9)	74 (79.6)	75 (83.3)	99 (94.3)	62 (83.8)	38 (82.6)	30 (93.8)	163 (89.6)	0.004
Thienopyridine	37 (31.1)	24 (18.6)	12 (12.9)	22 (24.4)	8 (7.6)	5 (6.8)	13 (28.3)	6 (18.8)	43 (23.6)	<0.001
Antiplatelet, Any	116 (97.5)	121 (93.8)	84 (90.3)	76 (84.4)	101 (96.2)	62 (83.8)	45 (97.8)	32 (100.0)	171 (94.0)	<0.001
DAPT	37 (31.1)	25 (19.4)	5 (5.4)	24 (26.7)	12 (11.4)	7 (9.5)	7 (15.2)	4 (12.5)	48 (26.4)	<0.001
Coumadin Derivatives	13 (10.9)	4 (3.1)	4 (4.3)	12 (13.3)	3 (2.9)	15 (20.3)	2 (4.3)	3 (9.4)	6 (3.3)	<0.001
Statin Therapy	106 (89.1)	115 (89.1)	39 (41.9)	60 (66.7)	72 (68.8)	62 (83.8)	19 (41.3)	23 (71.9)	152 (83.5)	<0.001
Beta-blockers	105 (88.2)	91 (70.5)	49 (52.7)	77 (85.6)	74 (70.5)	60 (81.1)	42 (91.3)	32 (100.0)	154 (84.6)	<0.001
ARB or ACE Inhibitors	58 (48.7)	65 (50.4)	40 (43.0)	61 (67.8)	57 (54.3)	27 (36.5)	20 (43.5)	20 (62.5)	94 (51.6)	0.005
Calcium Channel Blockers	11 (9.2)	10 (7.8)	31 (33.3)	19 (21.1)	25 (23.8)	10 (13.5)	5 (10.9)	8 (25.0)	41 (22.5)	<0.001
Amiodarone	29 (24.4)	18 (14.0)	16 (17.2)	8 (8.9)	13 (12.4)	1 (1.4)	5 (10.9)	2 (6.3)	19 (10.4)	<0.001
Cardiac glycoside	5 (4.2)	4 (3.1)	0	1 (1.1)	0	3 (4.1)	0	2 (6.3)	1 (0.5)	0.032
Diuretics	58 (48.7)	60 (46.4)	57 (61.3)	51 (56.7)	33 (31.4)	29 (39.2)	11 (23.9)	9 (28.1)	46 (25.3)	<0.001
H2-receptors blockers	10 (8.4)	5 (3.9)	81 (87.1)	9 (10.0)	22 (21.0)	1 (1.4)	0	26 (81.3)	35 (19.2)	<0.001

Abbreviations as in supplemental Table 1. DAPT, dual antiplatelet treatment; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme inhibitor. Values are shown as n/N (%).

Supplemental Table 5. Adjusted outcomes by countries, relative to the USA.

	UK	IT	GE	FR	NL	BE	HU	Other
OUTCOME at 5-year ALL								
MACCE	0.96 (0.69-1.33)	0.95 (0.67-1.34)	1.07 (0.76-1.51)	0.71 (0.51-1.00)	0.93 (0.62-1.37)	1.02 (0.65-1.61)	0.95 (0.61-1.50)	0.64 (0.47-0.87)
Composite Safety	1.27 (0.83-1.96)	0.96 (0.60-1.53)	1.49 (0.95-2.33)	0.76 (0.47-1.23)	1.40 (0.86-2.29)	1.37 (0.76-2.47)	0.91 (0.45-1.84)	0.78 (0.51-1.19)
Repeat Revascularization	0.68 (0.44-1.06)	0.99 (0.65-1.53)	0.78 (0.49-1.24)	0.59 (0.38-0.91)	0.66 (0.38-1.14)	0.85 (0.48-1.52)	1.08 (0.65-1.78)	0.54 (0.37-0.80)
OUTCOME at 5-year PCI								
MACCE	0.96 (0.62-1.47)	1.07 (0.69-1.66)	1.18 (0.71-1.76)	0.60 (0.37-0.98)	1.08 (0.65-1.80)	1.30 (0.71-2.37)	1.54 (0.88-2.70)	0.81 (0.54-1.22)
Composite Safety	0.95 (0.55-1.67)	0.75 (0.41-1.39)	1.22 (0.68-2.17)	0.45 (0.22-0.89)	1.24 (0.67-2.29)	1.36 (0.64-2.89)	0.84 (0.33-2.10)	0.66 (0.38-1.14)
Repeat Revascularization	0.80 (0.46-1.39)	1.38 (0.82-2.31)	0.96 (0.53-1.71)	0.70 (0.39-1.26)	0.92 (0.47-1.81)	1.52 (0.74-3.10)	1.89 (1.14-3.42)	0.87 (0.53-1.43)
OUTCOME at 5-year CABG								
MACCE	0.72 (0.38-1.34)	1.07 (0.57-2.03)	1.28 (0.67-2.44)	1.03 (0.55-1.93)	0.86 (0.39-1.88)	0.22 (0.03-1.66)	0.75 (0.27-2.07)	0.80 (0.44-1.43)
Composite Safety	1.48 (0.63-3.47)	1.52 (0.63-3.69)	2.38 (1.03-5.67)	1.44 (0.60-3.49)	1.41 (0.49-4.00)	0.65 (0.08-5.42)	1.27 (0.26-6.20)	1.45 (0.64-3.29)
Repeat Revascularization	0.32 (0.12-0.85)	1.03 (0.43-2.46)	0.65 (0.24-1.75)	0.84 (0.35-2.04)	0.85 (0.30-2.43)	0.82 (0.26-1.84)	0.69 (0.23-2.06)	0.65 (0.29-1.46)

Abbreviations as in supplemental Table 1. MACCE, major adverse cardiac and cerebrovascular events.

*Adjusted for male gender, age, body mass index, medically treated diabetes, peripheral vascular disease, creatinine blood level > 200 micromol/L, medically treated hypertension, medically treated hyperlipidemia, carotid artery disease, unstable angina, prior myocardial infarction, congestive heart failure, pulmonary hypertension, moderate left ventricular ejection fraction 30-49%, left main disease and number of lesions. Values are shown HR (95% CI).

*Patients in PCI group were additionally adjusted for the number of stents implanted, total stent length implanted, staged procedure, LAD treated, the number of overlapping stents, bi/trifurcation treated and incomplete revascularization.

*Patients in CABG group were additionally adjusted for bypass time, off-pump procedure, left internal mammary artery use, bilateral internal mammary artery use, complete arterial revascularization, the number of grafts and number of distal anastomoses and incomplete revascularization.

Supplemental Table 6. Multivariable predictors of adverse events in the overall cohort.

	HR (95% CI)	P-Value
MACCE		
PCI treatment vs. CABG	1.32 (1.11-1.57)	0.002
Age (per 5-yr increase)	1.10 (1.05-1.15)	<0.001
Medical treated diabetes	1.22 (1.01-1.47)	0.037
Peripheral vascular disease	1.98 (1.55-2.53)	<0.001
Unstable angina	1.24 (1.03-1.49)	0.020
Pulmonary hypertension	2.08 (1.14-3.80)	0.017
SYNTAX score (per 3 score increase)	1.03 (1.01-1.05)	0.009
Enrolment in France	0.71 (0.54-0.93)	0.012
Enrolment in group of other countries	0.66 (0.52-0.82)	0.001
Composite safety endpoint of death/stroke/MI		
Age	1.05 (1.03-1.06)	<0.001
Previous MI	1.33 (1.05-1.68)	0.016
SYNTAX score (per 3 score increase)	1.04 (1.01-1.07)	0.007
Enrolment in France	0.65 (0.45-0.95)	0.026
Enrolment in group of other countries	0.65 (0.48-0.87)	0.004
Repeat revascularization		
PCI treatment vs. CABG	1.78 (1.41-2.25)	<0.001
Medical treated diabetes	1.33 (1.05-1.69)	0.019
Peripheral vascular disease	1.49 (1.04-2.17)	0.028
Enrolment in the USA	1.65 (1.22-2.22)	0.001
Enrolment in Italy	1.59 (1.14-2.21)	0.006
Enrolment in Hungary	1.63 (1.06-2.51)	0.027

Abbreviations as in supplemental Table 1.

Supplemental Table 7. Multivariable predictors of adverse events in the PCI group.

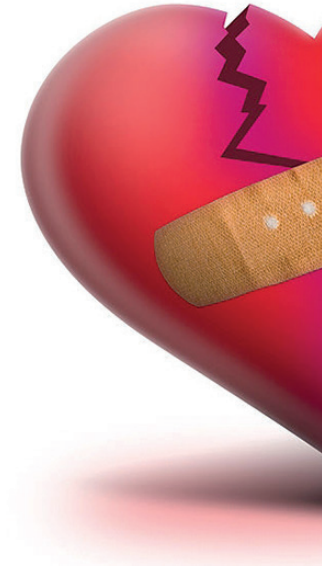
	HR (95% CI)	P-Value
MACCE		
Age (per 5-yr increase)	1.08 (1.02-1.14)	0.012
Medical treated diabetes	1.46 (1.15-1.86)	0.002
Peripheral vascular disease	1.47 (1.03-2.09)	0.032
Unstable angina	1.40 (1.11-1.78)	0.005
Enrolment in France	0.57 (0.38-0.84)	0.005
Incomplete Revascularization	1.32 (1.06-1.64)	0.015
No. of implanted stents	1.26 (1.12-1.41)	<0.001
Bi/Trifurcation treated, any	1.30 (1.02-1.65)	0.036
Composite safety endpoint of death/stroke/MI		
Age (per 5-yr increase)	1.19 (1.10-1.29)	<0.001
Peripheral vascular disease	2.12 (1.42-3.18)	<0.001
Previous MI	1.67 (1.24-2.24)	0.001
SYNTAX score (per 3 score increase)	1.06 (1.02-1.10)	0.001
Enrolment in France	0.52 (0.30-0.90)	0.020
Repeat revascularization		
Medical treated diabetes	1.69 (1.27-2.25)	<0.001
Pulmonary hypertension	3.53 (1.45-8.62)	0.005
Left main disease	1.45 (1.09-1.94)	0.012
Enrolment in Hungary	1.83 (1.07-3.10)	0.026
Incomplete revascularization	1.49 (1.13-1.95)	0.004
No. of implanted stents	1.33 (1.16-1.53)	<0.001

Abbreviations as in supplemental Table 1.

Supplemental Table 8. Multivariable predictors of adverse events in the CABG group.

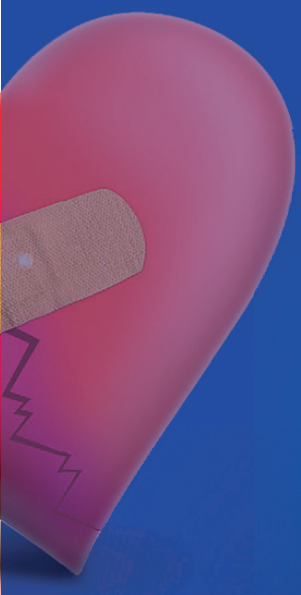
	HR (95% CI)	P-Value
MACCE		
Age (per 5-yr increase)	1.10 (1.02-1.20)	0.024
Peripheral vascular disease	2.25 (1.50-3.37)	<0.001
Previous MI	1.37 (2.02-1.03)	0.048
No. of distal anastomoses	0.79 (0.65-0.96)	0.018
Composite safety endpoint of death/stroke/MI		
Age (per 5-yr increase)	1.38 (1.22-1.57)	<0.001
Peripheral vascular disease	2.08 (1.27-3.41)	0.004
Medically treated hypertension	1.77 (1.02-3.09)	0.043
No. of implanted grafts	0.70 (0.51-0.95)	0.022
Repeat revascularization		
Age (per 5-yr increase)	1.12 (1.01-1.26)	0.031
Left main disease	1.69 (1.06-2.68)	0.028
Enrolment in the UK	0.42 (0.19-0.92)	0.030

Abbreviations as in supplemental Table 1.



Part 3

Improving Outcomes in Cardiac Surgery



Chapter 15

Compliance with guideline-directed medical therapy in contemporary coronary revascularization trials

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ABSTRACT

BACKGROUND: Despite the well-established benefits of secondary cardiovascular prevention, the importance of concurrent medical therapy in clinical trials of coronary revascularization is often overlooked.

OBJECTIVES: The goal of this study was to assess compliance with guideline-directed medical therapy (GDMT) in clinical trials and its potential impact on the comparison between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

METHODS: The Cochrane Central Register of Controlled Trials and MEDLINE were searched from 2005 to August 2017. Clinical trial registries and reference lists of relevant studies were also searched. Randomized controlled trials comparing PCI with drug-eluting stents versus CABG and reporting medical therapy after revascularization were included. The study outcome was compliance with GDMT, defined as the following: 1) any antiplatelet agent plus beta-blocker plus statin (GDMT1); and 2) any antiplatelet agent plus beta-blocker plus statin plus angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (GDMT2). Data collection and analysis were performed according to the methodological recommendations of The Cochrane Collaboration.

RESULTS: From a total of 439 references, 5 trials were included based on our inclusion and exclusion criteria. Overall, compliance with GDMT1 was low and decreased over time from 67% at 1 year to 53% at 5 years. Compliance with GDMT2 was even lower and decreased from 40% at 1 year to 38% at 5 years. Compliance with both GDMT1 and GDMT2 was higher in PCI than in CABG at all time points. Meta-regression suggested an association between lower use of GDMT1 and adverse clinical outcomes in PCI versus CABG at 5 years.

CONCLUSIONS: Compliance with GDMT in contemporary clinical trials remains suboptimal and is significantly lower after CABG than after PCI, which may influence the comparison of clinical trial endpoints between those study groups.

INTRODUCTION

Guideline-directed medical therapy (GDMT) is recommended by evidence-based guidelines for all patients with coronary artery disease (CAD). In addition to being considered the first line of treatment for patients with stable CAD, GDMT as secondary prevention after coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (1,2) is associated with a significant reduction in mortality and myocardial infarction (MI) risk (3). Moreover, GDMT alone may achieve a greater reduction in mortality than the choice of revascularization strategy (4).

However, currently available evidence suggests that compliance with GDMT remains poor after coronary revascularization, particularly after CABG (5–8) and in patients with comorbidities such as chronic renal disease. This poor compliance further increases patients' already higher risk of adverse outcomes (9). Moreover, randomized controlled trials (RCTs) of coronary revascularization, which are the primary source of evidence to guide contemporary clinical practice, often provide scant information regarding concurrent medical treatment (10). Therefore, whether the poor compliance with GDMT reported in population-based studies is also reflected in clinical trials and to what extent different compliance rates influence clinical outcomes between PCI and CABG remain unknown. The aims of the present study were as follows: 1) to analyze compliance with GDMT in landmark clinical trials of coronary revascularization; 2) to compare compliance with GDMT in PCI versus CABG; and 3) to assess its potential association with clinical trial outcomes.

METHODS

STUDY DESIGN. We performed a systematic review and meta-analysis according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (11) and The Cochrane Collaboration (12).

SEARCH STRATEGY. The Cochrane Central Register of Controlled Trials in the Cochrane Library and MEDLINE in PubMed were searched from 2005 to August 2017. This search was complemented by handsearching reference lists of relevant studies and clinical trial registries (August 2017). We did not apply limits by publication language, status, or date. Further details on search strategies are described in the protocol and the Supplemental Appendix.

SELECTION CRITERIA. RCTs comparing PCI with drug-eluting stents versus CABG in patients with CAD were included in the study. (Inclusion and exclusion criteria are specified in the Supplemental Appendix.)

DEFINITION OF OUTCOMES. GDMT was defined in 2 different categories: 1) GDMT1, a combination of any antiplatelet agent, beta-blocker, and statin; and GDMT2, a combination of any antiplatelet agent, beta-blocker, statin, and angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB).

STUDY SELECTION AND DATA COLLECTION. Two review authors independently screened all identified references according to pre-defined inclusion criteria. Full-text articles of those references were retrieved and reviewed for final inclusion according to prespecified inclusion and exclusion criteria. Disagreements were resolved by consensus.

Authors of the included trials were invited to provide individual patient data for the main classes of GDMT: aspirin, adenosine diphosphate $P2Y_{12}$receptor inhibitor, beta-blocker, statin, and ACE inhibitor and/or ARB. Data regarding clinical outcomes were obtained from published trial reports. One author collated outcome data into a master database and performed quality assessment, with a second author verifying its accuracy.

Compliance rates were calculated for individual drug classes and GDMT1 and GDMT2 as the number of patients prescribed each drug divided by the total number of patients with follow-up at each specific time point. Analysis was performed for patients undergoing PCI and CABG by computing compliance rates for each group. We used the absolute risk reduction as the effect measure, and differences in compliance rates and clinical outcomes were calculated by subtracting those of CABG from those of PCI. The time points selected for analysis were as follows: discharge, 1 year, 3 years, and 5 years.

Table 1. Summary of Large, Multicenter RCTs Comparing PCI Versus CABG in Patients Undergoing Revascularization for Complex CAD.

Trial (Ref. #)	Date	Sitew	Study Period	Population	Number of Patients	Interventions	Primary Endpoint	Outcome*			
								Follow-Up (yrs)	PCI (%)	CABG (%)	p Value
SYNTAX (27)	2013	85 centers in the United States and Europe	2005–2007	3-VD or LMS	1,800	PCI with first-generation paclitaxel-eluting stent vs. CABG(1:1ratio)	All-cause death, stroke, myocardial infarction, and repeat revascularization	1	17.8	12.4	0.002
								5	37.3	26.9	<0.001
FREEDOM (28)	2012	140 international centers	2005–2010	Diabetes and multivessel coronary artery disease (3-VD or LMS)	1,900	PCI with sirolimusor paclitaxel-eluting stents vs. CABG (1:1 ratio)	All-cause death, nonfatal myocardial infarction, or nonfatal stroke	2	13.0	11.9	0.005
								5	26.6	18.7	0.005
PRECOMBAT (29)	2015	13 centers in South Korea	2005–2009	LMS	600	PCI with sirolimus-eluting stent vs.CABG(1:1 ratio)	All-cause death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization	1	8.7	6.7	0.01
								5	17.5	14.3	0.26
BEST (30)	2015	27 centers in East Asia	2008–2013	Multivessel coronary artery disease (3-VD or LMS)	880	PCI with everolimuseluting stent vs. CABG (1:1 ratio)	All-cause death, myocardial infarction, or target-vessel revascularization	2	11.0	7.9	0.32
								4.6 (median)	15.3	10.6	0.04
EXCEL (31)	2016	126 centers in 17 countries	2010–2014	LMS with low/ intermediate SYNTAX scores	1,905	PCI with everolimuseluting stent vs. CABG (1:1 ratio)	All-cause death, stroke, or myocardial infarction	3	15.4	14.7	0.98

*Outcome for primary endpoint.

3-VD, 3-vessel disease; BEST, Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EXCEL, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; LMS, left main stem disease; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; RCT, randomized controlled trial; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

RISK OF BIAS ASSESSMENT. Risk of bias of individual studies was assessed according to the recommendations of The Cochrane Collaboration (12), taking into account the following items: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data addressed (attrition bias); andselective reporting (reporting bias).

STATISTICAL ANALYSIS AND EVIDENCE SYNTHESIS. Meta-analysis was conducted to assess the pooled compliance with GDMT in all the trials and to compare intervention groups (PCI vs. CABG). Outcomes and effect measures were reported as untransformed proportion and risk difference with 95% confidence intervals, respectively. The overall meta-analytical effect size was estimated by using the random effects model and the restricted maximum likelihood method. Chi-square Q statistics and I^2 statistics were used to assess heterogeneity. Meta-regression with a random effects model was performed to assess the impact of compliance with GDMT on clinical outcomes at 5 years. Overall trial data (and not individual patient data) were used, and only trials with 5-year follow-up were included in meta-regression. All statistical analyses were performed using the software Open MetaAnalyst (13). A p value <0.05 was considered statistically significant for all analyses.

RESULTS

STUDY SELECTION. The study search strategy yielded 749 references, of which 395 were excluded after screening. A total of 46 papers were reviewed, and 18 RCTs ultimately met the inclusion criteria. However, after reviewing the full papers, only 5 were included for analysis (Supplemental Figure 1).

Thirteen RCTs were excluded:

- MASS II (Medicine, Angioplasty, or Surgery Study) trial (14) and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (15) compared medical therapy versus revascularization with either PCI or CABG;
- VA CARDS (Coronary Artery Revascularization in Diabetes trial) (16) had serious methodological limitations (recruitment was stopped after enrolling only 25% of the intended sample size);

- SIMA (Stenting versus Internal Mammary Artery grafting) trial (17), BARI (Bypass Angioplasty Revascularization Investigation trial) (18), LE MANS (Left Main Coronary Artery Stenting trial) (19), SoS (Stent or Surgery trial) (20), ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery Trial) (21), and CARDia (Coronary Artery Revascularization in Diabetes) trial (22) used bare-metal stents;
- The MICASA (Myocardial Injury Following Coronary Artery Surgery Versus Angioplasty) trial (23) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) (24) did not collect data regarding medical therapy; and Two other trials were excluded because they did not collect data regarding medical therapy during follow-up (25,26).

Therefore, the following trials were included in the final analysis:

- SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial (27);
- FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (28);
- PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial (29);
- BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial (30); and
- EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (31).

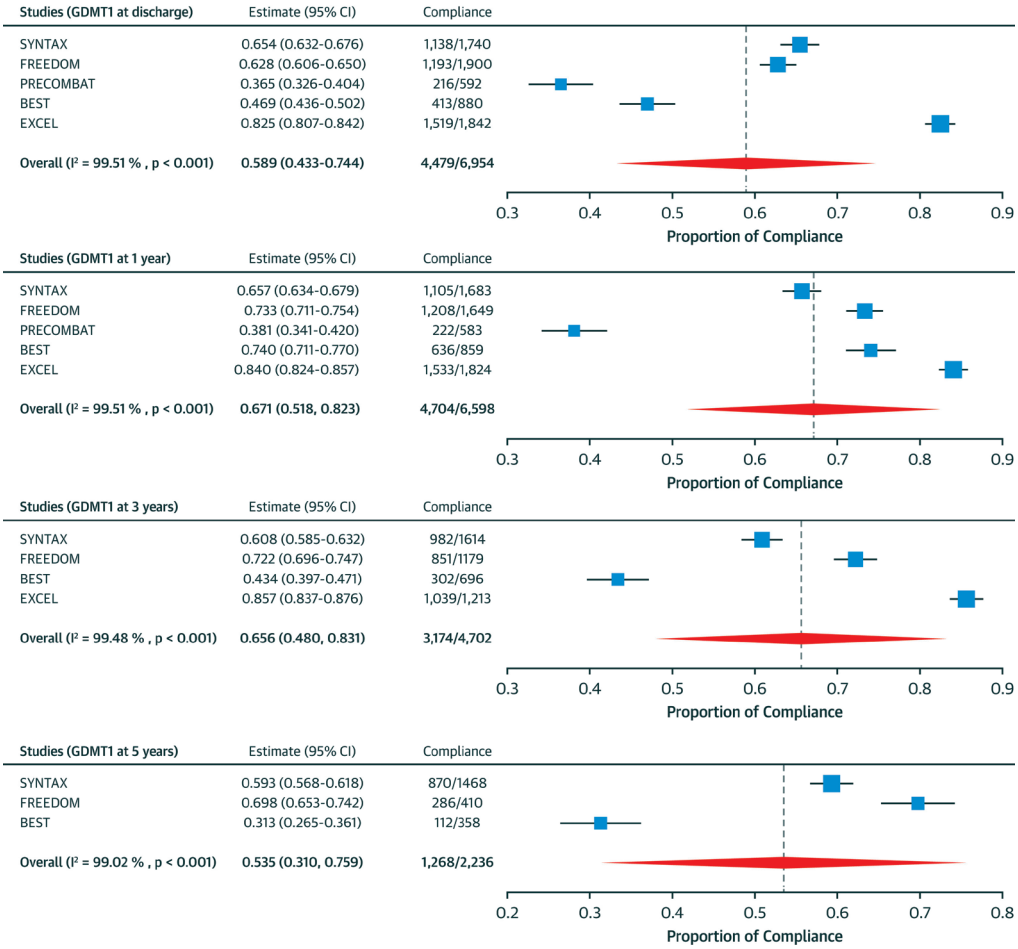


Figure 1. Compliance With GDMT1, Defined as Any Antiplatelet Agent þ Beta-Blocker þ Statin, in All Clinical Trials Over Time. Proportion of compliance calculated as number of patients prescribed guideline-directed medical therapy (GDMT) 1 divided by the total number of patients at each time point. BEST, Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; CI, confidence interval; EXCEL, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

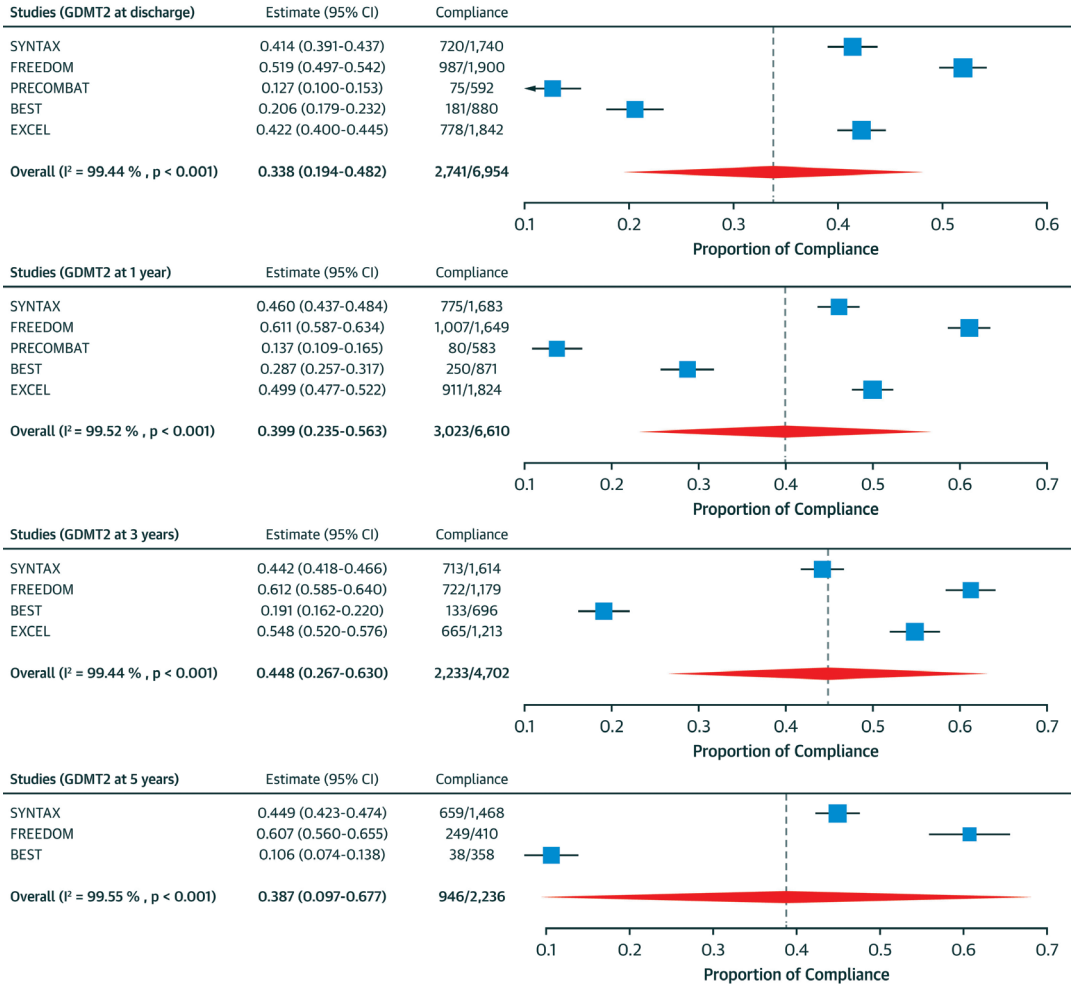


Figure 2. Compliance With GDMT2, Defined as Any Antiplatelet Agent þ Beta-Blocker þ Statin þ ACE Inhibitor or ARB, in All Clinical Trials Over Time. Proportion of compliance calculated as number of patients prescribed GDMT2 divided by the total number of patients at each time point. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; other abbreviations as in Figure 1.

An additional 2 surgical trials (CORONARY (CABG Off or On Pump Revascularization Study) (32) and ART (Arterial Revascularisation Trial) (33)) were added due to their relevance in the field of coronary revascularization and the availability of data on medical therapy. These trials were analyzed separately because they did not compare PCI versus CABG (Supplemental Figures 2 and 3, Supplemental Table 1).

STUDY CHARACTERISTICS. The 6 studies included in this review were all large, multicenter RCTs that compared PCI versus CABG in patients undergoing revascularization for complex CAD (Table 1). All those studies were considered landmark trials that provide the evidence basis for contemporary practice of coronary revascularization.

RISK OF BIAS WITHIN STUDIES. All the studies included in this review were RCTs of high methodological quality (Supplemental Table 2).

OVERALL COMPLIANCE WITH GDMT. Figures 1 and 2 illustrate compliance to GDMT1 and GDMT2, respectively, over time in all the trials. Data regarding individual drug classes are available in Supplemental Table 3. There was substantial variability between studies in both GDMT1 and GDMT2, as noted by the high I^2 values at each time point.

COMPLIANCE WITH GDMT IN PCI VERSUS CABG GROUPS. The Central Illustration and Figure 3 illustrate the difference between PCI and CABG in the proportion of compliance with GDMT1 and GDMT2, respectively, over time. For all studies except EXCEL with GDMT1, compliance was higher with PCI than with CABG. Data regarding individual drug classes are provided in Supplemental Table 4.

COMPLIANCE WITH GDMT AND CLINICAL OUTCOMES. Figure 4 illustrates the inverse association between the difference in compliance with GDMT1 at 5 years and the difference in clinical outcomes (all-cause mortality, MI, and a composite endpoint of all-cause mortality, MI, and stroke) for clinical trials with 5-year follow-up. As compliance with GDMT increased in the PCI group relative to the CABG group, the better outcomes of CABG became less evident. There was no difference in clinical outcomes when compliance for PCI exceeded that of CABG by approximately 8%.

Data for all other trials and time points are available in Supplemental Table 5. There was no apparent association between compliance with GDMT2 and clinical outcomes.

DISCUSSION

Despite the compelling benefits demonstrated by GDMT as secondary prevention after coronary revascularization, compliance remains low even in the tightly controlled environment of clinical trials. Furthermore, in our study, compliance with GDMT was higher in patients undergoing PCI compared with patients undergoing CABG, which may skew the comparison of clinical endpoints between those revascularization strategies.

OVERALL COMPLIANCE WITH GDMT. Overall compliance with aspirin and statins was high and reasonably stable over time, but there was some variation among trials, with compliance rates ranging from 75% to 95%. Some of the lack of compliance with aspirin may be related to intolerance to aspirin and/or concurrent use of anticoagulation therapy. Nonetheless, compliance with at least 1 antiplatelet agent was close to 100% in most trials throughout follow-up. Although aspirin intolerance or hypersensitivity can affect up to 10% of the population, there are currently rapid desensitization protocols that can be used in patients requiring dual antiplatelet therapy (34). Conversely, prevention of aspirin resistance has justified consideration of high-dose aspirin (325 mg daily) instead of low-dose aspirin (81 mg daily), but its benefits remain uncertain (35).

The differences in the use of adenosine diphosphate $P2Y_{12}$-receptor inhibitors may be related to whether dual antiplatelet therapy was used and for how long after revascularization. Considering the controversy regarding dual antiplatelet therapy after coronary revascularization (36–38), the significant differences between trials are not unexpected, particularly when considering surgical trials (CORONARY and ART). Although dual antiplatelet therapy is recommended after PCI, its benefit after CABG remains uncertain and is only recommended in specific circumstances (e.g., off-pump surgery) (35).

Compliance with beta-blockers and ACE inhibitors/ ARBs was lower and more variable, ranging from 43% to 80% and 28% to 79%, respectively. These findings are in keeping with previous reports from real-world registries (3). One possible explanation is the fact that although the efficacy of antiplatelet agents and statins

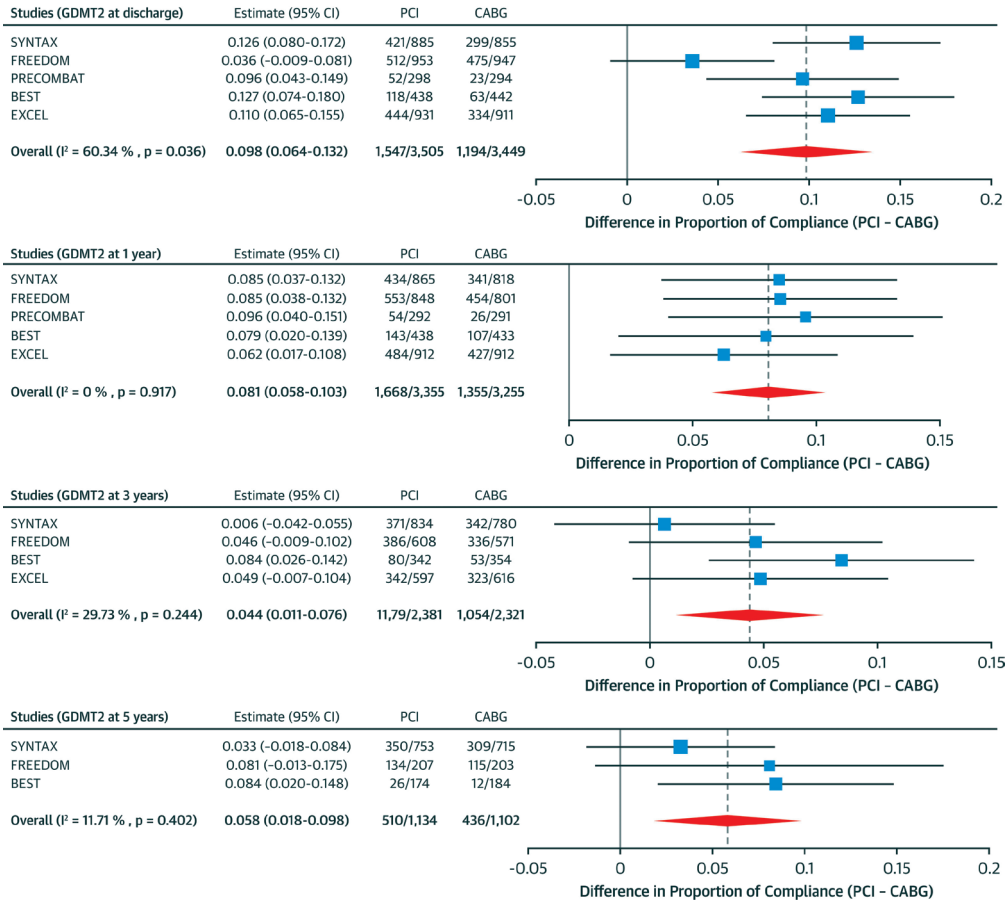


Figure 3. Compliance With GDMT2, Defined as Any Antiplatelet Agent þ Beta-Blocker þ Statin þ ACE Inhibitor or ARB, for PCI and CABG. Difference in compliance calculated by subtracting proportion of compliance in coronary artery bypass grafting (CABG) from proportion of compliance in percutaneous coronary intervention (PCI). Abbreviations as in Figures 1 and 2.

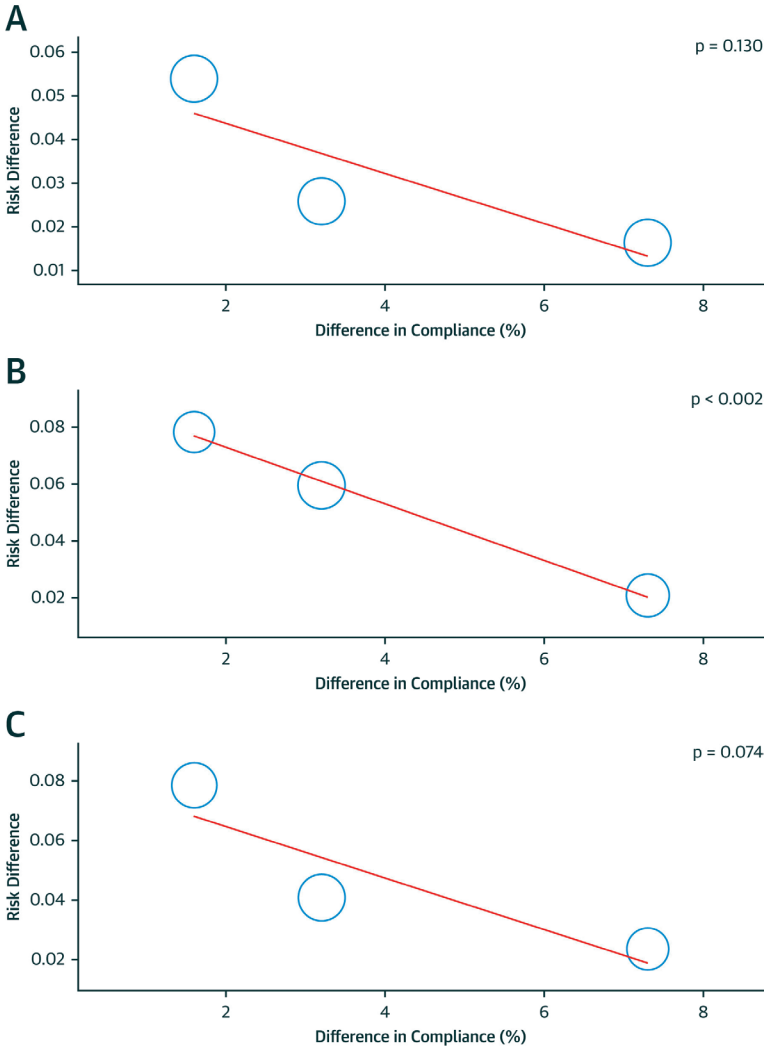


Figure 4. Meta-Regression Relating Compliance With GDMT1 (Any Antiplatelet Agent þ Beta-Blocker þ Statin) at 5 Years and Clinical Trial Outcomes at 5 Years. (A) Mortality, **(B)** myocardial infarction (MI), and **(C)** a composite of death, MI, and stroke. Only 3 trials were included (SYNTAX, FREEDOM, and BEST) because the others did not report 5-year outcomes. The x-axis represents the difference in compliance with GDMT1 between PCI and CABG; the y-axis represents the difference in clinical outcomes between PCI and CABG. As the difference in compliance favoring PCI widens, the superiority of CABG in terms of clinical outcomes decreases. The p value is for comparison between PCI and CABG. The size of the circles reflects the weight of the study. Abbreviations as in Figures 1 and 3.

in reducing cardiovascular events after coronary revascularization has long been recognized (1,39,40), the advantages of other drug classes have been established more recently (41) and may vary according to comorbidities and risk factors. Indeed, ACE inhibitors/ARBs are not routinely recommended after CABG unless in the presence of hypertension, diabetes, left ventricular systolic dysfunction, and chronic kidney disease (35,41), due to a potential increase in postoperative complications (42). In addition, controversies regarding the adverse effects of beta-blockers and statins may influence prescribing decisions (43–45).

Variability between trials was also found regarding compliance with GDMT1 and GDMT2. Although there was significant heterogeneity, even the highest compliance rates were unsatisfactory, as <40% of the patients were taking all the guideline-recommended drugs at 1 year. Furthermore, there was a modest decline in compliance over time. Although this outcome has been documented in the real world, more stable compliance was expected in this study due to the stricter follow-up required by clinical trial protocols (46).

The underuse of GDMT, particularly after CABG (8), is likely multifactorial. It may be related to underestimation of the importance of GDMT and the misconception that the value of maintaining GDMT is reduced once diseased coronary arteries have been mechanically revascularized with either PCI or CABG (47–49). In keeping with this, medical therapy is often neglected in coronary revascularization trials and hence poorly reported or not even collected at all, as happened in the recent NOBLE trial (24). On the contrary, GDMT compliance seemed higher in patients undergoing PCI than in those treated without revascularization (50,51), likely because hospital admission, often precipitated by an acute coronary event, provided an opportunity to reconsider prescription of cardioprotective medication. The conflicting evidence currently available calls for further studies to elucidate the factors related to GDMT noncompliance.

Irrespective of the underlying reasons, poor compliance with medical therapy that has demonstrated compelling benefits for secondary prevention in landmark clinical trials is a matter of concern. Considering that clinical trials operate within a strictly controlled environment and include a highly selected population of patients, drug compliance would be expected to be optimal. Furthermore, clinical trials provide the evidence to support current clinical practice and emphasize ideal standards. Therefore, optimizing compliance to GDMT is paramount to improve compliance and outcomes in everyday practice.

COMPARISON OF COMPLIANCE BETWEEN PCI AND CABG. Compliance with GDMT was consistently lower for patients undergoing CABG compared with PCI. The difference was particularly marked for $P2Y_{12}$ receptor inhibitors, as dual antiplatelet therapy is formally recommended in the guidelines after PCI (41). In contrast, aspirin and statins were identically used in both groups, and beta-blockers were more common in the CABG group in the EXCEL trial, perhaps due to their potential utility in preventing or treating post-operative atrial fibrillation (52).

Compliance with GDMT1 and GDMT2 was also better in the PCI group compared with the CABG group, with a difference close to 10% at 1 year for GDMT2. The underlying reasons are difficult to identify. The common although erroneous assumption that more complete revascularization after CABG obviates the need for further medical therapy cannot be overlooked. Medical therapy, particularly antiplatelet agents (53) and statins (54), reduces platelet activation, endothelial dysfunction, oxidative stress, and inflammation, which have all been associated with the development and progression of atherosclerosis (55–57), which is itself the primary mechanism leading to graft failure, particularly in venous grafts (58). Conversely, the lower compliance with ACE inhibitors/ARBs may be based on evidence suggesting that these drugs have no impact on midterm mortality or recurrent ischemia after CABG (59). Concerns about the detrimental effect of ACE inhibitors/ARBs on renal function and hyperkalemia in the post-operative period further compound the lower compliance with these drugs. However, this theory remains highly controversial (42,60,61), and the benefit of these drugs after the first 3 months has been compellingly demonstrated (62–64).

Another potential explanation for the low overall compliance with GDMT and the variability observed between individual trials is the high cost of medicines. Cost-effectiveness analyses support this possibility and imply that providing full coverage for secondary prevention therapy may save lives and decrease consumption of health care resources (65,66). Cardiovascular drugs are not easily affordable in many countries, particularly in South America and Southeast Asia. Therefore, in trials in which standard medication was not provided by the study team, the low compliance rates may reflect patients' inability to access expensive drugs. Although we could not analyze compliance rates stratified according to country, the hypothesis that the high price of cardiovascular medication significantly limits compliance in clinical trials deserves further investigation.

INFLUENCE OF GDMT ON CLINICAL TRIAL OUTCOMES. Our data suggest that there is a correlation between the difference in compliance rates and clinical outcomes when comparing PCI and CABG at 5 years. The better outcomes achieved with CABG versus PCI became less obvious as the compliance with GDMT increased in PCI versus CABG. Therefore, if compliance rates were identical in both groups, the superiority of CABG for major clinical endpoints might have been even more marked, as part of the benefit of PCI might be explained by better compliance with GDMT. However, because the population of patients included in each trial was different, the influence of confounding factors cannot be excluded. In addition, the correlation between GDMT1 and clinical outcomes was not corroborated by a similar correlation with GDMT2. Nevertheless, the importance of this hypothesis deserves consideration. Although some might argue that the varying profiles of medical therapy in PCI and CABG is part of the difference in the "strategies" of PCI and CABG, a fair and accurate comparison between PCI and CABG cannot be appreciated unless medical therapies are equalized with both approaches. Other than for dual antiplatelet therapy, single antiplatelet treatment, beta-blockers, and statins seem advantageous irrespective of the revascularization strategy.

STUDY LIMITATIONS. In this study, medication prescription was considered as a surrogate for medication adherence, which may have resulted in overestimating true compliance rates. Medication nonadherence is a well-recognized issue in cardiovascular disease and may be responsible for approximately 125,000 preventable deaths every year as only about one-half of the patients consistently take prescribed medications (67). In addition, in this study, it was impossible to assess whether treatment doses were appropriate and to ascertain the reasons for noncompliance because this factor was not tracked in any of the randomized trials. Finally, the meta-regression relating compliance to subsequent outcomes was based on only 3 studies and compliance data at one point in time, adding imprecision to the results. We did not have access to individual patient-level data in the present analysis, which would have been superior to meta-regression in linking compliance with outcomes.

CONCLUSIONS

Although GDMT is crucial for patients to derive the most benefit from coronary revascularization, compliance was low even in landmark randomized clinical trials. Moreover, drug compliance was consistently lower in the CABG group compared with the PCI group, and this difference may have influenced the differences in major clinical outcomes between groups. Further research is warranted to delineate the extent to which different rates of compliance with GDMT after PCI compared with CABG influence the relative shortand longterm outcomes with these revascularization modalities.

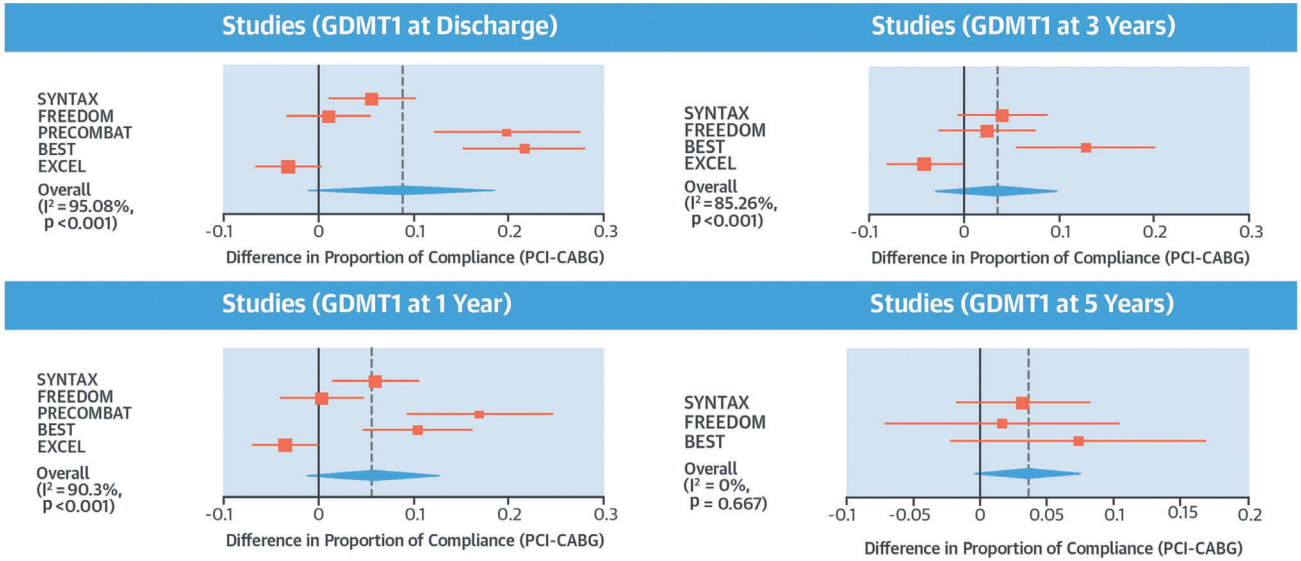
The potential consequences of poor compliance with GDMT on long-term clinical outcomes are substantial. Therefore, a pressing need exists to develop effective strategies to improve compliance with lifesaving drugs. Clinical trials have an important role to play by serving as an example of ensuring outstanding compliance with GDMT.

CLINICAL PERSPECTIVES

COMPETENCY IN PRACTICE-BASED LEARNING AND IMPROVEMENT: Compliance with GDMT in contemporary clinical trials is suboptimal and lower in trials of patients undergoing CABG than in those investigating PCI.

TRANSLATIONAL OUTLOOK: More concerted efforts are needed to improve compliance with GDMT among patients participating in clinical trials of coronary revascularization and to understand the impact of compliance on the comparative outcomes of patients undergoing percutaneous or surgical coronary revascularization.

CENTRAL ILLUSTRATION: Compliance With GDMT1, Defined as Any Antiplatelet Agent + Beta-Blocker + Statin, for PCI and CABG



Central illustration. Compliance With GDMT1, Defined as Any Antiplatelet Agent þ Beta-Blocker þ Statin, for PCI and CABG. Pinho-Gomes, A.-C. et al. J Am Coll Cardiol. 2018;71(6):591–602. Difference in compliance calculated by subtracting proportion of compliance in coronary artery bypass grafting (CABG) from proportion of compliance in percutaneous coronary intervention (PCI). BEST, Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; EXCEL, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; GDMT1, guideline-directed medical therapy 1; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

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SUPPLEMENTAL MATERIAL

Protocol

Objectives

- To analyse compliance with GDMT in landmark clinical trials of coronary revascularisation;
- To compare adherence to GDMT in PCI versus CABG;
- To assess its potential association with clinical trial outcomes.

Methods

Study question

- Population – patients undergoing coronary artery revascularisation
- Intervention – percutaneous coronary intervention
- Comparison – coronary artery bypass surgery
- Outcome – compliance with GDMT

Eligibility criteria

- Randomised controlled trials;
- Including patients with complex coronary artery disease;
- Comparing percutaneous coronary intervention and coronary artery bypass surgery;
- Reporting compliance with the different drug classes recommended by guidelines as secondary cardiovascular prevention;

Exclusion criteria

- PCI performed using bare metal stents (BMS), because they have been replaced by DES which are now standard practice and routinely used unless there are specific contraindications; trials in which BMS were commonly used are now considered 'historical' as they do not influence contemporary coronary revascularisation;
- Minimally-invasive CABG;
- Comparison of medical therapy versus early revascularisation as this would have a significant interference with our outcome of interest which is compliance with medical therapy after coronary revascularisation. We considered that medical therapy could not be simultaneously intervention and outcome;
- When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports will be included for quantitative assessment at each time interval;
- No exclusion criteria based on language of publication will be used.

Information sources

- Bibliographic databases
  - √ Medline or PubMed
  - √ The Cochrane Central Register of Controlled Trials (CENTRAL)
- Clinical trials registries
- Grey literature databases (conference abstracts)
- Reference lists in other reviews and guidelines
- Contact with authors

Search strategy

Query definition

- PubMed/Medline

((("Angioplasty, Balloon, Coronary"(MeSH Terms) OR "Percutaneous Coronary Intervention"(MeSH Terms)) AND ("Coronary Artery Bypass"(MeSH Terms) OR "Coronary Disease/surgery"(MeSH Terms) OR "Coronary Vessels/surgery"(MeSH Terms) OR "Myocardial Infarction/surgery"(MeSH Terms))) AND ("randomized controlled trial"(Publication Type) AND random*(tiab) AND trial(tiab))) AND ("2005"(PDAT) : "3000"(PDAT))

- CENTRAL

#1 MeSH descriptor: (Angioplasty, Balloon, Coronary) explode all trees 3747

#2 MeSH descriptor: (Percutaneous Coronary Intervention) explode all trees 5100

#3 MeSH descriptor: (Coronary Artery Bypass) explode all trees 5556

#4 MeSH descriptor: (Coronary Disease) explode all trees and with qualifier(s): (Surgery - SU) 1855

#5 MeSH descriptor: (Coronary Vessels) explode all trees and with qualifier(s): (Surgery - SU) 208

#6 MeSH descriptor: (Myocardial Infarction) explode all trees and with qualifier(s): (Surgery - SU) 538

#7 randomized controlled trial:pt (Word variations have been searched) 426390

#8 random*:ti,ab,kw (Word variations have been searched) 620177

#9 trial:ti,ab,kw (Word variations have been searched) 561361

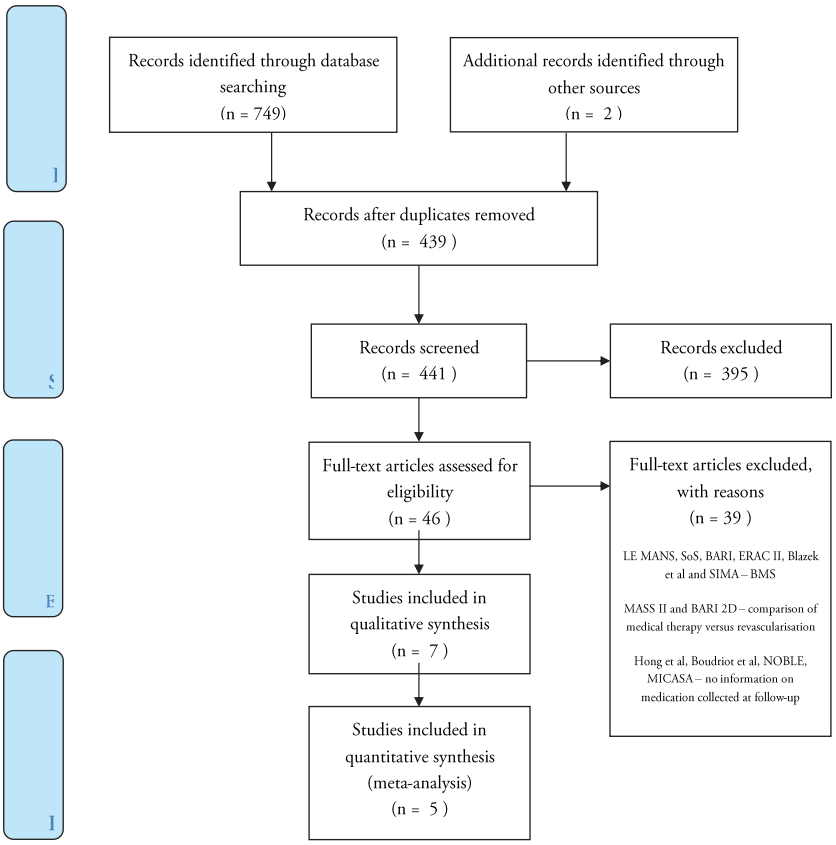
#10 (#1 or #2) and (#3 or #4 or #5 or #6) and (#7 and #8 and #9) Publication Year from 2005 416

Study records

- Data management – database will be created in Excel with documentation of reason for exclusion
- Selection process – screening of titles and abstracts by two independent reviewers; eligibility assessment of full-text manuscripts by two independent reviewers; disagreements will be resolved by consensus.
- Data collection process – one investigators will collect data and a second investigator will confirm its accuracy against trial reports. Investigators of the original studies will be contacted to obtain missing data.

Risk of bias in individual studies

One investigator will perform quality assessment using specific criteria for RCT as recommended by Cochrane.



Supplemental Figure 1. PRISMA flow chart

Supplemental Table 1. Data for CORONARY and ART trials.

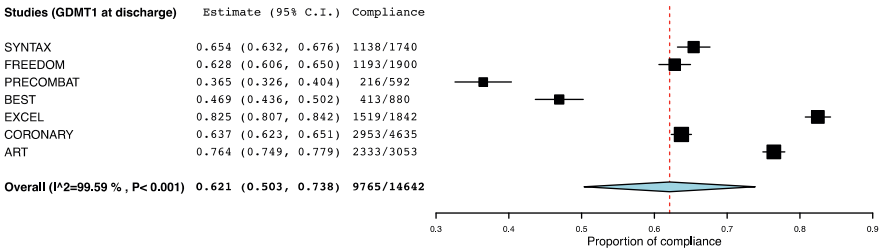
Trial	Date	Site	Study period	Population	Number patients	Interventions	Primary endpoint	Follow-up	Primary endpoint outcome (%)		p-value
CORONARY	2016	79 centres in 19 countries	2006-2011	Patients undergoing isolated CABG surgery	4752	ONCABG vs OPCABG (1:1 ratio)	All-cause death, nonfatal stroke, nonfatal myocardial infarction, or new renal failure requiring dialysis	5 years	23.1 (off-pump)	23.6 (on-pump)	0.72
ART	2016	28 centres in seven countries	2004-2007	Patients undergoing isolated CABG surgery	3102	BIMA vs SIMA grafting (1:1 ratio)	All-cause death, myocardial infarction, or stroke	5 years	12.2 (SIMA)	12.7 (BIMA)	0.69

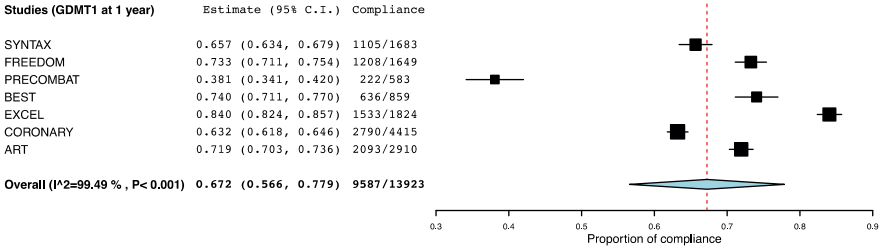
Supplemental Table 2. Quality assessment.

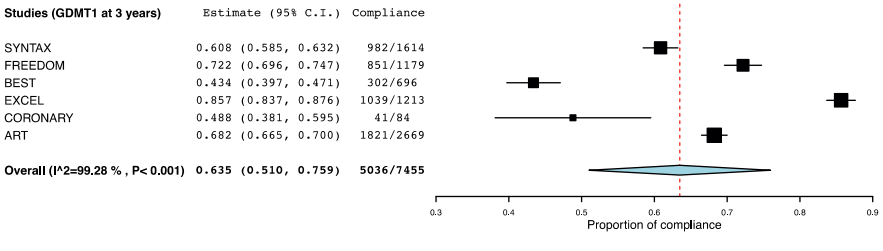
Trials	SYNTAX (1)	FREEDOM (2)	PRECOMBAT (3)	BEST (4)	EXCEL (5)	CORONARY (6)	ART (7)
Random sequence generation (selection bias)	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated	Low risk Patients were randomly allocated
Allocation concealment (selection bias)	Low risk Central allocation service using Interactive Voice Response System	Low risk Allocation done using permuted blocks with dynamic balancing within each study centre	Low risk Central allocation using an interactive Web-based response system	Low risk Central allocation service using an interactive Web-response system with random block sizes and stratification by centre	Low risk Central allocation service using Interactive Voice Response System or Web-based system	Low risk Central allocation service using a 24-hour automated voice-activated telephone randomisation service	Low risk Central allocation via telephone call; sequence generated with randomly varying block sizes and stratified by centre
Blinding of participants and personnel (performance bias)	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding	Low risk No blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding	Low risk No blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding

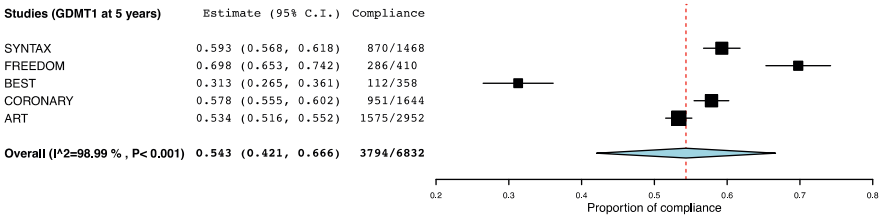
Supplemental Table 2. Continued.

Incomplete outcome data addressed (attrition bias)	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis	Low risk Minimal loss of follow-up and missing outcome data balanced in numbers across intervention groups; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias	The study appears to be free of other sources of bias

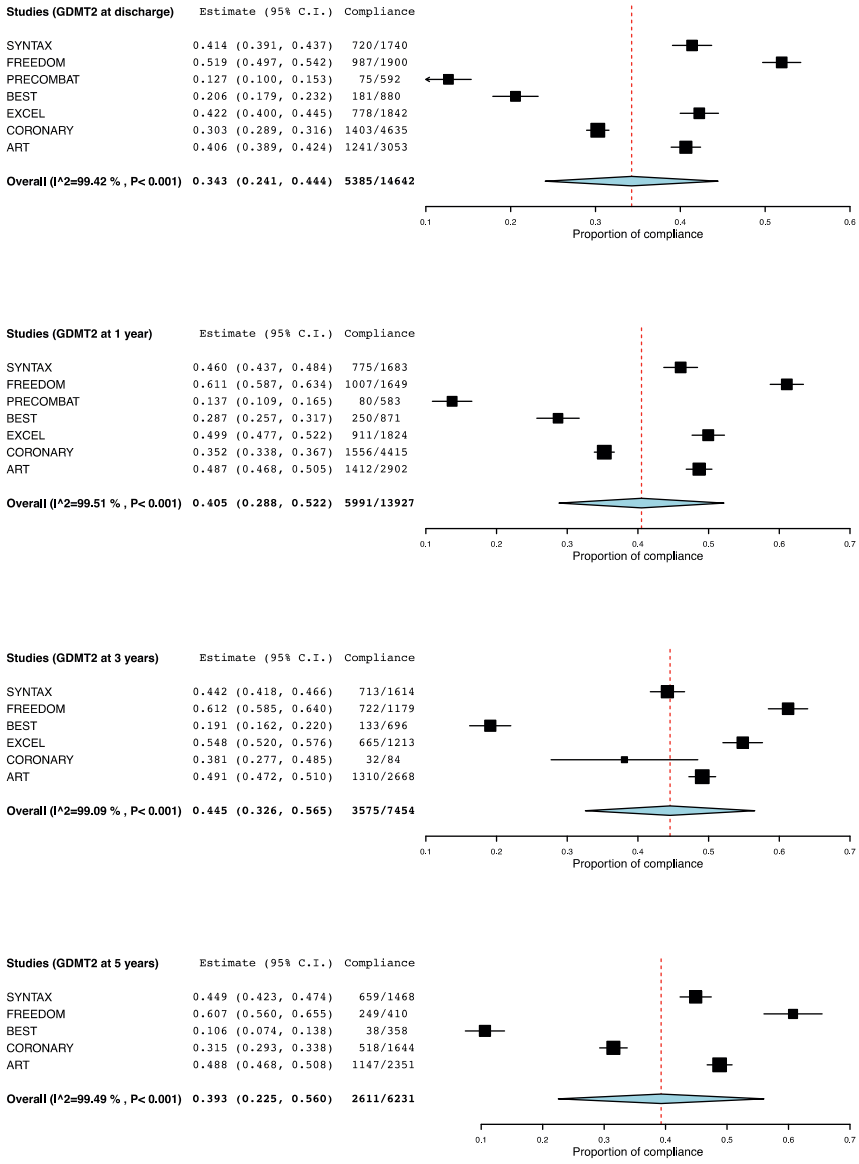








Supplemental Figure 2. Compliance with guideline-directed medical therapy 1 (GDMT1), defined as any antiplatelet agent + beta-blocker + statin, in all clinical trials over time. Proportion of compliance calculated as number of patients prescribed GDMT divided by the total number of patients at each time point.



Supplemental Figure 3. Compliance with guideline-directed medical therapy 2 (GDMT2), defined as any antiplatelet agent + beta-blocker + statin + angiotensin-converting inhibitor or angiotensin receptor blocker, in all clinical trials over time. Proportion of compliance calculated as number of patients prescribed GDMT divided by the total number of patients at each time point.

Supplemental Table 3. Results.

ASPIRIN	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1557	1740	89.5	1485	1683	88.2				1325	1614	82.1				1227	1468	83.6
FREEDOM	1723	1900	90.7	1751	1867	93.8	1579	1651	95.6	1424	1483	96.0	1115	1179	94.6	747	793	94.2	384	410	93.7
PRECOMBAT	477	596	80.0	569	599	95.0	531	551	96.4												
BEST	746	865	86.2	852	880	96.8	798	859	92.9	744	795	93.6	574	696	82.5	467	564	82.8	276	358	77.1
EXCEL	1836	1855	99.0	1790	1822	98.2	1729	1801	96.0	1616	1698	95.2	1137	1207	94.2						
CORONARY	3386	4751	71.3	4169	4728	88.2	3764	4415	85.3	24	48	50.0	36	57	63.2	277	377	73.5	1287	1644	78.3
ART	2619	3102	84.4	2917	3053	95.5	2676	2910	92.0	2591	2821	91.8	2442	2674	91.3	2208	2450	90.1	2228	2356	94.6
P12Y2 INHIBITOR	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				998	1740	57.4	738	1683	43.9				385	1614	23.9				320	1468	21.8
FREEDOM	474	1900	24.9	1529	1867	81.9	1259	1649	76.3	608	1483	41.0	414	1179	35.1	225	793	28.4	119	410	29.0
PRECOMBAT	408	596	68.5	495	599	82.6	392	551	71.1												
BEST	637	865	73.6	818	880	93.0	675	859	78.6	482	795	60.6	373	696	53.6	253	564	44.9	181	355	51.0
EXCEL	1184	1855	63.8	1206	1842	65.5	1003	1824	55.0	808	1718	47.0	527	1210	43.6						
CORONARY	1577	4656	33.9	1460	4635	31.5	1080	4415	24.5	7	48	14.6	7	56	12.5	96	377	25.5	353	1644	21.5
ART	784	3102	25.3	699	3053	22.9	366	2910	12.6	277	2821	9.8	252	2674	9.4	246	2447	10.1	233	2353	9.9
ANY ANTIPLATELET	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1637	1740	94.1	1566	1683	93.0				1448	1615	74.0				1299	1467	88.5
FREEDOM	1762	1910	92.3	1854	1867	99.3	1617	1649	98.1	1458	1483	98.3	1153	1179	80.9	775	793	97.7	403	410	98.3
PRECOMBAT	485	596	81.4	573	596	96.1	542	582	93.1												
BEST	765	880	86.9	864	880	98.2	840	859	97.8	778	836	93.1	648	696	50.3	527	564	93.4	327	358	91.3
EXCEL	1841	1855	99.2	1813	1842	98.4	1772	1824	97.1	1666	1718	97.0	1178	1213	90.4						
CORONARY	3535	4656	75.9	4349	4635	93.8	4058	4415	91.9	33	48	68.8	39	56	77.4	321	377	85.1	1446	1644	88.0
ART	2724	3102	87.8	3032	3053	99.3	2801	2909	96.3	2716	2821	96.3	2548	2674	75.8	2311	2450	94.3	2199	2356	93.3
BETA-BLOCKER	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1369	1740	78.7	1315	1683	78.1				1194	1614	74.0				1086	1468	74.0
FREEDOM	1429	1900	75.2	1477	1867	79.1	1357	1651	82.2	1226	1483	82.7	954	1179	80.9	624	793	78.7	326	410	79.5
PRECOMBAT	131	596	22.0	303	599	50.6	282	551	51.2												
BEST	459	865	53.1	489	880	55.6	737	859	85.8	473	795	59.5	350	696	50.3	252	564	44.7	155	358	43.3
EXCEL	1584	1855	85.4	1618	1840	87.9	1631	1814	89.9	1542	1713	90.0	1096	1212	90.4						
CORONARY	3659	4751	77.0	3819	4728	80.8	3453	4415	78.2	46	76	60.5	65	84	77.4	431	571	75.5	1195	1644	72.7
ART	2548	3102	82.1	2552	3053	83.6	2323	2910	79.8	2184	2821	77.4	2027	2674	75.8	1855	2446	75.8	1793	2355	76.1
STATIN	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1423	1740	81.8	1415	1683	84.1				1334	1614	82.7				1232	1468	83.9
FREEDOM	1564	1900	82.3	1566	1867	83.9	1473	1649	89.3	1347	1483	90.8	1063	1179	90.2	721	793	90.9	369	410	90.0
PRECOMBAT	248	596	41.6	380	599	63.4	411	551	74.6												
BEST	556	865	64.3	733	880	83.3	753	859	87.7	676	795	85.0	547	696	78.6	440	564	78.0	276	358	77.1
EXCEL	1731	1855	93.3	1740	1840	94.6	1743	1810	96.3	1655	1716	96.4	1173	1212	96.8						
CORONARY	3643	4751	76.7	3800	4728	80.4	3668	4415	83.1	38	76	50.0	53	85	62.4	492	569	86.5	1363	1644	82.9
ART	2994	3102	96.5	2820	3053	92.4	2726	2910	93.7	2624	2821	93.0	2488	2674	93.0	2269	2450	92.6	2180	2356	92.5
ACEI/ARB	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1028	1740	59.1	1111	1683	66.0				1097	1614	68.0				1044	1468	71.1

FREEDOM	1531	1900	80.6	1334	1867	71.5	1367	1651	82.8	1252	1483	84.4	978	1179	83.0	657	793	82.8	323	410	78.8
PRECOMBAT	117	596	19.6	148	599	24.7	154	551	27.9												
BEST	348	865	40.2	307	880	34.9	331	859	38.5	319	795	40.1	240	696	34.5	165	564	29.3	100	358	27.9
EXCEL	814	1855	43.9	912	1840	49.6	1048	1791	58.5	1029	1699	60.6	752	1200	62.7						
CORONARY	3023	4751	63.6	2536	4683	54.2	2318	4415	52.5	25	76	32.9	50	84	59.5	292	569	51.3	951	1644	57.8
ART	2068	3102	66.7	1553	3053	50.9	1960	2907	67.4	1963	2821	69.6	1895	2674	70.9	1736	2450	70.9	1700	2355	72.2
GDMT 1	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				1138	1740	65.4	1105	1683	65.7				982	1614	60.8				870	1468	59.3
FREEDOM	1193	1900	62.8				1208	1649	73.3	1118	1483	75.4	851	1179	72.2	558	793	70.4	286	410	69.8
PRECOMBAT	21	600	3.5	216	592	36.5	222	583	38.1												
BEST	339	880	38.5	413	880	46.9	636	859	74.0	426	795	53.6	302	696	43.4	197	564	34.9	112	358	31.3
EXCEL	1488	1855	80.2	1519	1842	82.5	1533	1824	84.0	1452	1718	84.5	1039	1213	85.7						
CORONARY	2295	4656	49.3	2953	4635	63.7	2790	4415	63.2	30	76	39.5	41	84	48.8	346	569	60.8	951	1644	57.8
ART	2112	3101	68.1	2333	3053	76.4	2093	2910	71.9	1992	2821	70.6	1821	2669	68.2	1638	2444	67.0	1575	2952	53.4
GDMT 2	Baseline			Discharge			1 year			2 years			3 years			4 years			5 years		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SYNTAX				720	1740	41.4	775	1683	46.0				713	1614	44.2				659	1468	44.9
FREEDOM	987	1900	51.9				1007	1649	61.1	937	1483	63.2	722	1179	61.2	472	793	59.5	249	410	60.7
PRECOMBAT	4	600	0.7	75	592	12.7	80	583	13.7												
BEST	175	880	19.9	181	880	20.6	250	871	28.7	180	795	22.6	133	696	19.1	83	564	14.7	38	358	10.6
EXCEL	693	1855	37.4	778	1842	42.2	911	1824	49.9	900	1718	52.4	665	1213	54.8						
CORONARY	1585	4656	34.0	1403	4635	30.3	1556	4415	35.2	19	76	25.0	32	84	38.1	191	569	33.6	518	1644	31.5
ART	1403	3100	45.3	1241	3053	40.6	1412	2902	48.7	1396	2819	49.5	1310	2668	49.1	1182	2443	48.4	1147	2351	48.8

Supplemental Table 4. Results.

Aspirin

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				93.8	85.0	8.8	91.4	84.8	6.6				81.5	82.7	-1.2				84.1	83.1	1.0
FREEDOM	91.0	90.4	0.6	99.0	88.4	10.7	96.8	94.4	2.4	95.3	96.8	-1.5	94.9	94.2	0.7				94.7	92.6	2.1
PRECOMBAT	84.1	75.1	9.0	97.6	91.9	5.6	97.7	94.7	3.1												
BEST	87.5	84.8	2.7	97.0	96.6	0.4	93.2	92.6	0.6	93.7	93.5	0.1	84.2	80.8	3.4	84.1	81.6	2.5	78.2	76.1	2.1
EXCEL	99.5	98.5	1.0	98.5	98.0	0.5	96.5	95.5	0.9	95.8	94.6	1.2	93.6	94.8	-1.2						

P12Y2 inhibitor

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				96.4	17.0	79.4	71.9	14.2	57.7				23.3	24.5	-1.2				31.5	11.6	19.9
FREEDOM	27.8	22.1	5.7	98.1	65.2	32.9	88.4	63.5	24.9	58.5	22.2	36.2	48.2	21.2	27.0				42.0	15.8	26.3
PRECOMBAT	74.3	61.3	13.0	92.7	70.6	22.1	84.4	54.3	30.1												
BEST	79.5	66.8	12.7	96.6	89.4	7.2	88.3	69.1	19.2	70.3	51.1	19.2	58.2	49.2	9.0	48.9	41.0	7.9	53.8	48.4	5.4
EXCEL	97.4	29.8	67.6	97.6	32.6	65.0	84.4	25.5	58.9	71.1	22.9	48.2	65.5	22.2	43.3						

Any antiplatelet

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				97.2	90.9	6.3	95.3	90.7	4.6				90.2	89.1	1.1				90.0	87.0	3.1
FREEDOM	93.0	91.5	1.4	99.5	99.1	0.3	98.5	97.6	0.8	98.3	98.3		98.4	97.2	1.2	97.3	98.1	-0.8	98.6	98.0	0.5
PRECOMBAT	85.3	76.6	8.7	98.2	93.7	4.5	95.3	90.5	4.8												
BEST	88.6	85.3	3.3	99.1	97.3	1.8	98.6	97.0	1.6	98.7	88.0	10.7	95.0	91.2	3.8	94.6	92.4	2.2	92.0	90.8	1.2
EXCEL	99.6	98.9	0.7	99.1	97.7	1.4	98.5	95.8	2.6	98.3	95.7	2.6	97.3	96.9	0.4						

Beta-blocker

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				78.4	78.9	-0.5	79.2	77.0	2.2				74.5	73.5	1.0				75.4	72.4	3.0
FREEDOM	75.8	74.7	1.1	79.8	78.4	1.5	82.2	82.2		82.6	82.8	-0.2	80.9	80.9					79.7	79.3	0.4
PRECOMBAT	21.4	22.7	-1.3	63.3	35.3	28.0	61.4	38.3	23.1												
BEST	51.5	54.9	-3.4	68.5	42.8	25.7	89.0	82.7	6.3	65.2	53.9	11.4	55.3	45.5	9.8	46.7	42.7	4.0	50.0	37.0	13.0
EXCEL	81.9	88.9	-7.1	83.4	92.5	-9.1	85.6	94.3	-8.7	85.2	94.9	-9.7	86.6	94.1	-7.5						

Statin

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				85.2	78.2	7.0	86.0	82.0	4.0				83.6	81.7	1.9				83.5	84.3	-0.8
FREEDOM	82.1	82.6	-0.5	84.3	83.5	0.8	89.2	89.5	-0.4	91.4	90.2	1.2	90.6	89.7	1.0				88.9	91.1	-2.2
PRECOMBAT	40.7	42.8	-2.1	63.9	62.9	1.0	72.1	77.8	-5.7												
BEST	59.7	69.6	-9.9	83.1	83.5	-0.4	89.9	85.5	4.5	87.1	83.0	4.0	81.9	75.4	6.4	80.8	75.3	5.4	79.3	75.0	4.3
EXCEL	95.4	91.2	4.2	96.7	92.4	4.2	96.9	95.7	1.3	97.0	95.9	1.0	97.8	95.8	2.1						

ACEI/ARB

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				66.2	51.7	14.5	68.3	63.6	4.8				66.9	69.1	-2.2				71.6	70.6	1.0
FREEDOM	80.6	80.6		80.7	62.0	18.7	88.5	76.8	11.6	86.5	82.2	4.2	85.7	80.0	5.7				88.4	69.0	19.4
PRECOMBAT	21.4	17.5	3.9	30.3	18.0	12.3	31.8	23.0	8.8												
BEST	40.5	39.9	0.6	44.5	25.3	19.2	41.3	35.8	5.5	44.7	35.7	9.0	36.3	32.8	3.5	32.2	26.4	5.9	34.5	21.7	12.7
EXCEL	52.9	34.7	18.2	56.8	42.2	14.7	62.5	54.5	8.0	65.0	56.1	8.9	66.6	58.9	7.7						

GDMT 1

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				68.1	62.6	5.6	68.6	62.6	6.0				62.8	58.7	4.1				60.8	57.6	3.2
FREEDOM	63.3	62.3	1.0				73.5	73.0	0.4	76.0	74.7	1.4	73.4	70.9	2.4	68.2	72.8	-4.6	70.5	69.0	1.6
PRECOMBAT	4.0	3.0	1.0	46.3	26.5	19.8	46.6	29.6	17.0												
BEST	38.8	38.2	0.6	58.0	36.0	22.0	79.3	68.8	10.5	60.2	47.1	13.0	50.0	37.0	13.0	37.0	33.0	4.0	35.1	27.7	7.3
EXCEL	79.3	81.1	-1.8	80.9	84.1	-3.2	82.3	85.7	-3.4	81.8	87.2	-5.4	83.6	87.7	-4.1						

GDMT 2

	BASELINE			DISCHARGE			1 YEAR			2 YEARS			3 YEARS			4 YEARS			5 YEARS		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX				47.6	35.0	12.6	50.2	41.7	8.5				44.5	43.8	0.6				46.5	43.2	3.3
FREEDOM	53.7	50.2	3.6				65.2	56.7	8.5	65.0	61.3	3.7	63.5	58.8	4.6	58.8	60.3	-1.5	64.7	56.7	8.1
PRECOMBAT	0.3	1.0	-0.7	17.4	7.8	9.6	18.5	8.9	9.6												
BEST	18.9	20.8	-1.9	26.9	14.3	12.7	32.6	24.7	7.9	27.2	18.2	9.0	23.4	15.0	8.4	17.4	12.2	5.2	14.9	6.5	8.4
EXCEL	44.4	30.3	14.1	47.7	36.7	11.0	53.1	46.8	6.3	54.8	49.9	4.9	57.3	52.4	4.9						

The numbers represent the percentage of patients compliant with each drug class at each time point.
Diff is the difference between percentage of compliance in patients undergoing PCI and CABG.
GDMT1 = any antiplatelet + beta-blocker + statin
GDMT2 = any antiplatelet + beta-blocker + statin + ACEI/ARB

Supplemental Table 5. Results.

GDMT 1

	GDMT 1			MORTALITY			MYOCARDIAL INFARCTION (MI)			DEATH, MI OR STROKE		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX 5Y	46.5	43.2	3.3	13.9	11.4	2.5	9.7	3.8	5.9	20.8	16.7	4.1
FREEDOM 5Y	64.7	56.7	8.1	16.3	10.9	5.4	13.9	6.0	7.9	26.6	18.7	7.9
PRECOMBAT 1Y	18.5	8.9	9.6	5.7	2.6	3.1	2.0	1.0	1.0	8.4	9.6	-1.2
BEST 5Y	14.9	6.5	8.4	6.6	5.0	1.6	4.8	2.7	2.1	11.9	9.5	2.4
EXCEL 3Y	57.3	52.4	4.9	8.3	6.0	2.3	8.1	8.7	-0.6	15.4	14.7	0.7

GDMT 2

	GDMT 2			MORTALITY			MYOCARDIAL INFARCTION (MI)			DEATH, MI OR STROKE		
	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff	PCI	CABG	Diff
SYNTAX 5Y	60.8	57.6	3.2	13.9	11.4	2.5	9.7	3.8	5.9	20.8	16.7	4.1
FREEDOM 5Y	70.5	69.0	1.6	16.3	10.9	5.4	13.9	6.0	7.9	26.6	18.7	7.9
PRECOMBAT 1Y	73.5	73.0	0.4	5.7	2.6	3.1	2.0	1.0	1.0	8.4	9.6	-1.2
BEST 5Y	35.1	27.7	7.3	6.6	5.0	1.6	4.8	2.7	2.1	11.9	9.5	2.4
EXCEL 3Y	83.6	87.7	-4.1	8.3	6.0	2.3	8.1	8.7	-0.6	15.4	14.7	0.7

The numbers represent the percentage of patients compliant with each drug class (column 1) and who had any of the clinical outcomes (columns 2 to 4).
GDMT1 = any antiplatelet + beta-blocker + statin
GDMT2 = any antiplatelet + beta-blocker + statin + ACEI/ARB

Chapter 16

Clinical guidelines on perioperative medication in adult cardiac surgery

Based on:

2017 EACTS Guidelines on perioperative medication in adult cardiac surgery

Sousa-Uva M, Head SJ, **Milojevic M**, Collet JP, Landoni G, Castella M, Dunning J, Gudbjartsson T, Linker NJ, Sandoval E, Thielmann M, Jeppsson, Landmesser U.

2017 EACTS/EACTA Guidelines on patient blood management in adult cardiac surgery

Pagano D, **Milojevic M**, Meesters MI, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Boer C.

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Eur J Cardiothorac Surg. 2018;53:79-111.

J Cardiothorac Vasc Anesth. 2018;32:88-120.

INTRODUCTION

Clinical guidelines are issued for areas where there is substantial evidence to support strong recommendations, usually derived from randomised clinical trials or large registries. Quality criteria for developing Clinical Guidelines require transparency on how they are formulated. The methodology manual for the EACTS clinical guidelines was issued to standardise the development process of evidence-based documents (1). Adult cardiac surgery is an essential therapeutic approach to reduce mortality and morbidity in appropriately defined patients. The outcome depends on the management of underlying conditions, and medical treatment is key in the optimal perioperative and long-term success of the cardiac surgery. Several studies have suggested that patients after coronary artery bypass grafting (CABG) benefit the most from risk-factor modifying strategies (2-6).

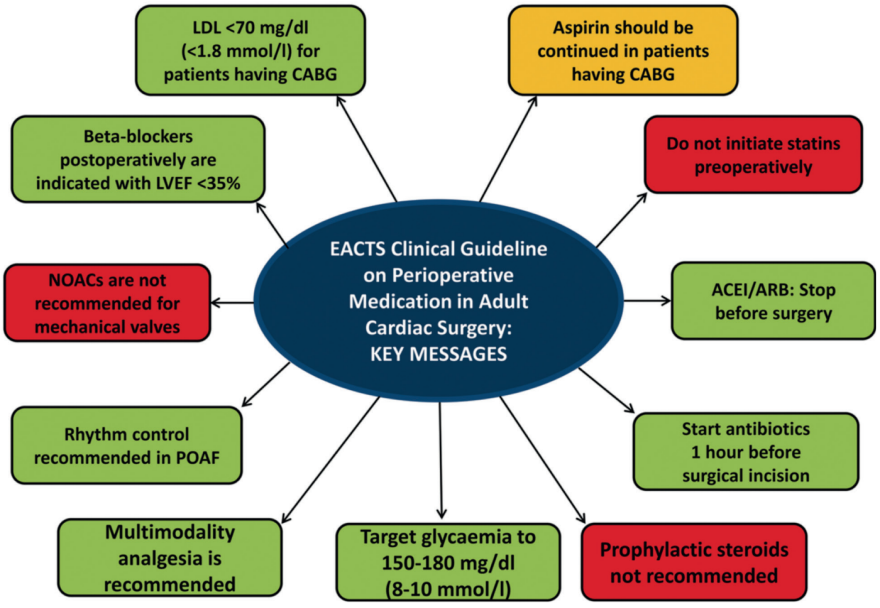
Medical therapy impacts on adult cardiac surgery at three distinct phases: preoperatively, intraoperatively and postoperatively (7). Preoperatively, drugs might need to be introduced or interrupted to decrease the odds of procedural complications. Intraoperatively, glycaemia control and prophylactic antibiotics are essential to reducing the risk of infectious complications. Postoperatively, restarting or initiating medication to prevent ischaemic events, prevent arrhythmias, and manage cardiovascular risk factors and heart failure is required to impact the long-term prognosis in a positive way, especially if they are included in a formal program of cardiac rehabilitation (8).

Cardiac surgery is always a major life event that is associated with increased disease awareness and represents a unique opportunity to introduce optimised medical therapy and stress the importance of lifestyle modifications, compliance with medication and lifelong follow-up. Surgical patients are often sub-optimally treated (9, 10) although the benefit of a more intense postoperative patient-based medication therapy on the outcome is established after cardiac surgery (10, 11).

The surgical community may be somewhat under-informed (12), although previous guidelines on specific drugs have been published (13-15). Therefore EACTS Clinical Guideline Committee has found that there is a need to produce an updated guideline focusing on the main pharmacological classes involved in the perioperative treatment and prevention of adverse events in patients undergoing adult cardiac surgery. Excluded are medications used for the treatment of surgery complications, such as graft vasospasm after CABG, perioperative ischemia, myocardial infarction (MI), low cardiac output syndrome (LCOS), renal failure,

arrhythmias except for atrial fibrillation (AF), pneumonia, wound infection, and neurological complications. The rationale behind excluding these topics from the final document is the fact that is comprehensively covered in other relevant clinical guidelines (16-22), or these surgical complications will be enclosed in the upcoming expert document. The following central illustration summarises what is new and what is essential in these guidelines according to a class of recommendation.

Central illustration with the main recommendations.



[a]At least 2 days before surgery in patients with normal renal function and 3-4 days before surgery in dabigatran-treated patients with impaired renal function. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; BB, beta-blockers; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction: NOAC, non-vitamin K antagonist oral anticoagulant; POAF, new onset atrial fibrillation.

ANTITHROMBOTIC MANAGEMENT

Antithrombotic treatment with anticoagulants and platelet inhibitors reduces the risk for thromboembolic complications but may increase the risk of intraoperative and postoperative bleeding complications. An individual assessment of the risk of thromboembolism and bleeding based on the medication, patient condition (elective, urgent or emergent), imaging results and planned surgical intervention is recommended within the Heart Team conference.

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is one of the cornerstones for the treatment of acute and chronic cardiovascular disease. Secondary prevention with ASA has been shown to reduce mortality, MI and cerebrovascular events in different subsets of patients with occlusive cardiovascular disease (23), but increases the risk of bleeding complications.

Discontinuation before surgery

A meta-analysis of 13 trials with 2,399 CABG patients comparing preoperative ASA administration versus no treatment or treatment with a placebo (24) showed that treatment with ASA reduced the risk of perioperative MI (odds ratio (OR) 0.56; 95% confidence interval (CI) 0.33–0.96) but without mortality reduction (OR 1.16; 95% CI 0.42–3.22). Postoperative bleeding, red cell transfusions and surgical re-exploration were increased with ASA. However, the included studies were of low methodological quality.

A recent large randomised controlled trial (RCT) compared the administration of ASA (100 mg) on the day of surgery versus the use of a placebo in CABG patients (25) and demonstrated no significant effect of ASA-treatment on thrombotic and bleeding perioperative events. However, included patients were only eligible if not using ASA preoperatively or stopped ASA at least four days before surgery. Therefore, a strategy of discontinuation vs. continuation was not evaluated.

Another RCT on pre-treatment demonstrated that a larger preoperative ASA dose (300 mg) was associated with increased postoperative bleeding but a lower rate of major cardiovascular events at a 53-month follow-up (26). Similarly, a small RCT reported that ASA pre-treated patients (300 mg) had significantly more postoperative bleeding (+25%), and this effect was more pronounced (+137%) in carriers of the glycoprotein IIIa allele PlA2 (27). Similar results were presented in a previous meta-analysis (28), where less bleeding was reported in patients

receiving <325 mg ASA daily. Of note, stopping ASA 5 days before surgery and replacing it with low molecular weight heparin (LMWH) increases the risk of bleeding complication, and therefore, should be abandoned (29).

In summary, the continuation of ASA is associated with more blood loss but less ischemic events during and after CABG surgery. Recent data suggest that the inhibiting effect of ASA on platelet aggregability is clearly susceptible to platelet transfusion (30, 31), which also argues for the continuation of ASA in CABG patients undergoing elective or urgent surgery. However, in patients who refuse blood transfusions, undergo non-coronary cardiac surgery or those at high risk of re-exploration for bleeding—such as complex and redo operations, severe renal insufficiency, haematological disease and hereditary platelet function deficiencies —ASA should be stopped at least five days before surgery (32). The increased risk of bleeding complications if ASA and other antithrombotic drugs are not discontinued must be weighed against the potentially increased risk for thrombotic complications during the preoperative cessation period.

Restart after surgery

In a large prospective observational trial (33), patients who restarted ASA within 48 hours of CABG had a mortality rate of 1.3% as compared with a rate of 4.0% among those who did not receive ASA during this period ($P<0.001$). ASA therapy was associated with a 48% reduction in the incidence of MI ($P<0.001$), a 50% reduction in the incidence of stroke ($P=0.01$), a 74% reduction in the incidence of renal failure ($P<0.001$), and a 62% reduction in the incidence of bowel infarction ($P=0.01$). A systematic review of seven studies shows that administration of ASA within six hours of CABG surgery is associated with improved graft patency without increased incidence of bleeding complications (34). Therefore, ASA should be given to all CABG patients as soon as there is no concern over bleeding.

P2Y12 inhibitors

Dual antiplatelet therapy (DAPT) with ASA and P2Y12-receptor inhibitors (clopidogrel, ticagrelor, prasugrel) (Table 1) reduces the risk of thrombotic complications in patients with acute coronary syndrome (ACS) compared to treatment with ASA only (35-37), especially if they undergo percutaneous coronary intervention (PCI). The risk of thrombotic complications is further reduced if one of the more potent third-generation P2Y12 inhibitors (ticagrelor or prasugrel) is used instead of clopidogrel (36, 37), at the expense of increased spontaneous and surgical bleeding complications (36, 38).

Table 1. P2Y12 inhibitors.

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Bioavailability	50%	80%	36%	100%
Half life (active metabolite)	1-2 hours	2-15 hours	7-9 hours	3-6 minutes
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Onset of action	2-6 hours	30 min	30 min	2 min
Frequency of administration	Once-daily	Once daily	twice-daily	Intravenous infusion
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hours
Antidote	No	No	No	No
Discontinuation before non-acute surgery	At least 5 days	At least 7 days	At least 3 days	1 hour

Discontinuation before surgery

Continuing DAPT until surgery increases the risk of bleeding, transfusions and re-exploration for bleeding, as shown in RCTs (39, 41), observational studies (42, 43) and meta-analyses (44, 45). It is, therefore, recommended that P2Y12-receptor inhibitors be discontinued before elective surgery whenever possible (7, 46). Alternatively, elective operations may be postponed until the DAPT treatment period is completed. In urgent cases—most often in patients with ACS—the risk of thromboembolic episodes (stent thrombosis, MI) while waiting for the effect of the P2Y12-receptor inhibitors to cease must be weighed against the risk of perioperative bleeding complications. In extreme high-risk patients for thrombotic events, e.g. recent stent implantation (47), bridging therapy may be considered (7, 46), or surgery may be performed without discontinuation of P2Y12 inhibitors. If bridging is warranted, GPIIb/IIIa inhibitors may be used. However, cangrelor, a new reversible intravenous P2Y12 inhibitor with ultrashort half-life has demonstrated a high rate of maintenance of platelet inhibition and no excessive perioperative bleeding complications (48, 49). However, cangrelor is not yet labelled for bridging.

Safe discontinuation intervals differ according to pharmacodynamics and pharmacokinetic profile of each P2Y12-receptor inhibitor (46). When P2Y12-receptor inhibitors are discontinued, ASA therapy should be continued until surgery. Discontinuation of clopidogrel five days of more before CABG did not increase the risk of bleeding complications (39). A longer time interval (7 days) is recommended for prasugrel due to a longer offset of platelet inhibition (50) and a higher incidence of CABG-related bleeding complications in comparison with clopidogrel (41). In patients treated with ticagrelor, discontinuation three to four days, as opposed to five days or more before CABG surgery, is not associated with

a higher incidence of bleeding complications (OR 0.93; 95% CI 0.53-1.64, *P*=0.80) (42). This has been confirmed in multiple studies (43, 51). It is unlikely that the optimal discontinuation period before surgery of any of the P2Y12 inhibitors will ever be tested in an RCT with clinically relevant endpoints.

Platelet function testing

Besides the variances in platelet inhibitory effect between different P2Y12 inhibitors, there is also a significant individual variation in the magnitude and duration of the antiplatelet effect (52-54). Residual platelet reactivity is a marker of both ischemic and bleeding events (55), but platelet function testing to adjust P2Y12 inhibition does not improve clinical outcome in low and high-risk patients (56, 57). Platelet function testing (PFT) may optimise the timing for surgical procedures especially in patients in whom the time since discontinuation is unclear (e.g. in unconscious or confused patients) or treatment compliance is unclear.

Bedside PFT has been suggested as an option to guide interruption of therapy rather than an arbitrarily specified period (7, 46). Preoperative ADP-mediated platelet aggregation predicts CABG-related bleeding complications in both clopidogrel (58, 61) and ticagrelor (54) treated ACS patients. A strategy based on preoperative PFT to determine the timing of CABG in clopidogrel-treated patients led to 50% shorter waiting time as compared to an arbitrary time-based discontinuation strategy (62). PFT in ACS patients eligible for CABG appears as a valuable approach to refine the timing of surgery. No RCT or observational study has compared perioperative bleeding complications between a fixed versus a PFT-based time delay from discontinuation to surgery. Furthermore, cut-off levels of P2Y12 inhibition to predict perioperative bleedings are not available for all PFT devices.

Restart after surgery

Current guidelines recommend DAPT for all ACS patients independently of revascularisation treatment (7, 46). This also applies to CABG patients or other non-coronary cardiac surgery. Furthermore, DAPT after CABG has been associated with reduced all-cause mortality (63, 64) and a better vein graft patency (OR 0.59; 95% CI 0.43–0.82) (64), although this evidence is conflicting. Potential benefits of DAPT after CABG are offset by an increased risk of bleeding complications.

The magnitude of benefit appears to be more pronounced in ACS over stable angina and with more potent P2Y12 inhibitors versus clopidogrel (63, 65), resulted in a reduction of mortality over 50% (40, 41). It is recommended to restart DAPT after CABG as soon as considered safe in patients with ACS. There is currently no evidence to support starting routine DAPT after CABG in patients not receiving DAPT preoperatively, although starting DAPT may be considered in patients with a higher ischemic risk due to a coronary endarterectomy or off-pump surgery.

The optimal timing should be as soon as deemed safe. In high ischemic risk patients, P2Y12-inhibitors should be restarted within 48 hours after surgery while it may be considered safe to postpone after three to four days when ischemic risk is low (e.g. stent implantation >1 month ago or ACS without stenting).

Glycoprotein IIb/IIIa inhibitors

GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) are today almost exclusively used in conjunction with PCI, but may also be used for bridging high-risk patients on oral P2Y12 inhibitors to surgery (7, 46, 66). The optimal time delay for discontinuation before surgery is mainly based on pharmacokinetic assumptions. Platelet function recovery is obtained within 24–48 hours of abciximab discontinuation, and up to 4–8 hours after eptifibatide and tirofiban discontinuation (67). However, the pooled analysis of patients from the EPILOG and EPISTENT trials show no difference between patients treated with abciximab and placebo in term of a major blood loss (88% vs. 79%, P=0.27) when the study treatment was stopped within 6 hours before surgical incision (68). In addition, other clinical studies suggesting that cessation 4h hours before surgery is sufficient for all GPIIB/IIIA inhibitors, including abciximab (66, 69).

PREOPERATIVE ANTICOAGULATION AND BRIDGING

In vitamin K antagonists (VKA)-treated patients (Table 2) (70, 71), VKAs should be stopped five days before planned elective surgery to achieve target international normalised ratio (INR) below 1.5 on the day of surgery. In non-vitamin K antagonist oral anticoagulants (NOACs)-treated patients undergoing elective surgery, NOACs should be discontinued before surgery with various time intervals according to renal function and type of drugs. In patients on direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban), treatment should be stopped ≥2 days before surgery (72). In dabigatran-treated patients with creatinine clearance <50mL/min/1.73 m^2, NOAC should be stopped ≥4 days before surgery.

Table 2. Vitamin K antagonists.

Molecule	Acenocoumarol	Coumadine (Warfarin)	Fluindione	Phenprocoumone
Half life	10 hours	35–80 hours	30–40 hours	3–4 days
Steady state	2–3 days	3–6 days	3–4 days	6 days
Initial dose	4mg	5mg	20mg	6mg
Duration of effect	2–4 days	4–5 days	2–3 days	4–5 days

The decision to bridge oral anticoagulation with unfractionated heparin (UFH) or LMWH depends on the ischaemic risk of underlying diseases. Preoperative bridging imposes a risk of perioperative bleeding, and therefore not all patients on anticoagulation undergoing cardiac surgery should be bridged (73). Therefore, bridging oral anticoagulation is recommended in patients with mechanical prosthetic heart valves, valvular AF (moderate-to-severe mitral stenosis), AF with a CHA_2DS_2-VASc score >4 or with a recent acute thrombotic event within the previous four weeks defined as ischemic stroke, ACS or pulmonary embolism (PE). Bridging should also be considered in patients with left ventricular apex thrombus, antithrombin 3, proteins C and S deficiency.

Bridging should be initiated according to the outline in Figure 1. UFH is the only approved bridging method although evidence is not randomised. Studies show that patients receiving preoperative UFH versus LMWH had less postoperative re-exploration for bleeding after cardiac surgery (74). However, UFH can only be administered in a hospital, while LMWH does not require hospital admission and continuous IV infusion. Therefore, LMWH is more practical and user-friendly and should be considered as an alternative for bridging with dose adjustment according to weight and renal function and if possible with monitoring of anti-Xa activity with a target of 0.5–1.0 U/mL. The option of bridging with fondaparinux is not recommended due to an extended half-life (17-21 hours) and the lack of an adequate antidote, although it may have a role in patients with a history of heparin-induced thrombocytopenia (75).

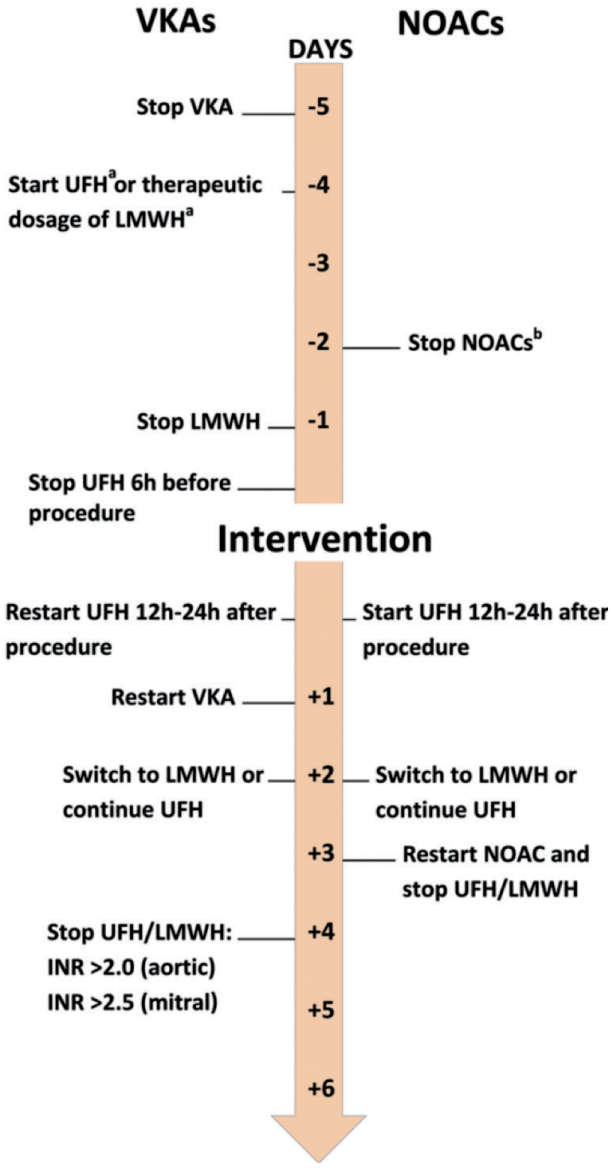


Figure 1. Management of oral anticoagulation in patients with an indication for preoperative bridging. INR, international normalised ratio; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonists; NOAC, non-vitamin K antagonist oral anticoagulant.

[a]Bridging with UFH/LMWH should start when INR values are below specific therapeutic ranges.

[b]Discontinuation should be prolonged to >72 hours if creatinine clearance is 50–79 ml/min/1.73 m^2, or ≥96 hours if creatinine clearance is <50 ml/min/1.73 m^2.

There is no adequate evidence to support substantiated time intervals for stopping preoperative bridging with UFH and LMWH. Based on the pharmacokinetics of UFH, it is recommended that administration be discontinued at least 6 hours preoperatively. Discontinuation of LMWH should occur >12 hours preoperatively, as suggested by studies reporting high plasma concentrations if it is given twice daily (76).

Table 3. Different types of direct oral anticoagulant agents.

	Apixaban	Dabigatran Etexilate	Edoxaban	Rivaroxaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Bioavailability	51–85%	6–8%	60%	80%
T_{max}	3 hours	2 hours	1–3 hours	2–4 hours
Half-life	9–14 hours	14–17 hours	5–11 hours	9–13 hours
Frequency of administration	Twice-daily	Once- or twice-daily	Once-daily	Once- or twice-daily
Renal excretion	25%	80%	36–45%	66% (half inactive)
Antidote	Andexanet alfa	Idarucizumab	Andexanet alfa	Andexanet alfa
Discontinuation before non-acute surgery	At least 48h	At least 48-96 hours[a]	At least 48h	At least 48h

[a]Discontinuation ≥48 hours if creatinine clearance is >80 ml/min/1.73 m^2, discontinuation >72 hours if creatinine clearance is 50–79 ml/min/1.73 m^2, and discontinuation ≥96 hours if creatinine clearance is <50 ml/min/1.73 m^2.

In the case of an urgent procedure, surgery should ideally be delayed. For the emergency surgical procedure, the benefit associated with surgery performed with a short delay should be balanced with the risk of major haemorrhage. When VKAs cannot be stopped for an appropriate time, prothrombin complex concentrate (PCC) (25 IU FIX kg) should be given with an additional administration of 5 mg of vitamin K1 (intravenous, subcutaneous or oral) (77). In the situation of patients taking NOACs (Table 3), it is requested that the timing between the last intake and the procedure be checked and the treatment concentration be assessed using specific diluted thrombin times (Haemoclot®) for dabigatran and anti-factor-Xa assays for the FXa inhibitors. The plasma concentration of NOACs should be considered the best way to assess the residual activity of the drug and estimate the bleeding risk (78). For dabigatran and rivaroxaban, surgery may be safely performed if the plasma concentration is below 30 ng/ml, while with higher concentrations surgery should be delayed for 12 hours (if the concentration is 30–200 ng/ml) or 24 hours (if the concentration is 200–400 ng/ml). If plasma concentrations are too high and surgery cannot be postponed, the off-label therapeutic use of both non-activated PCC (20–50 U/kg) and activated

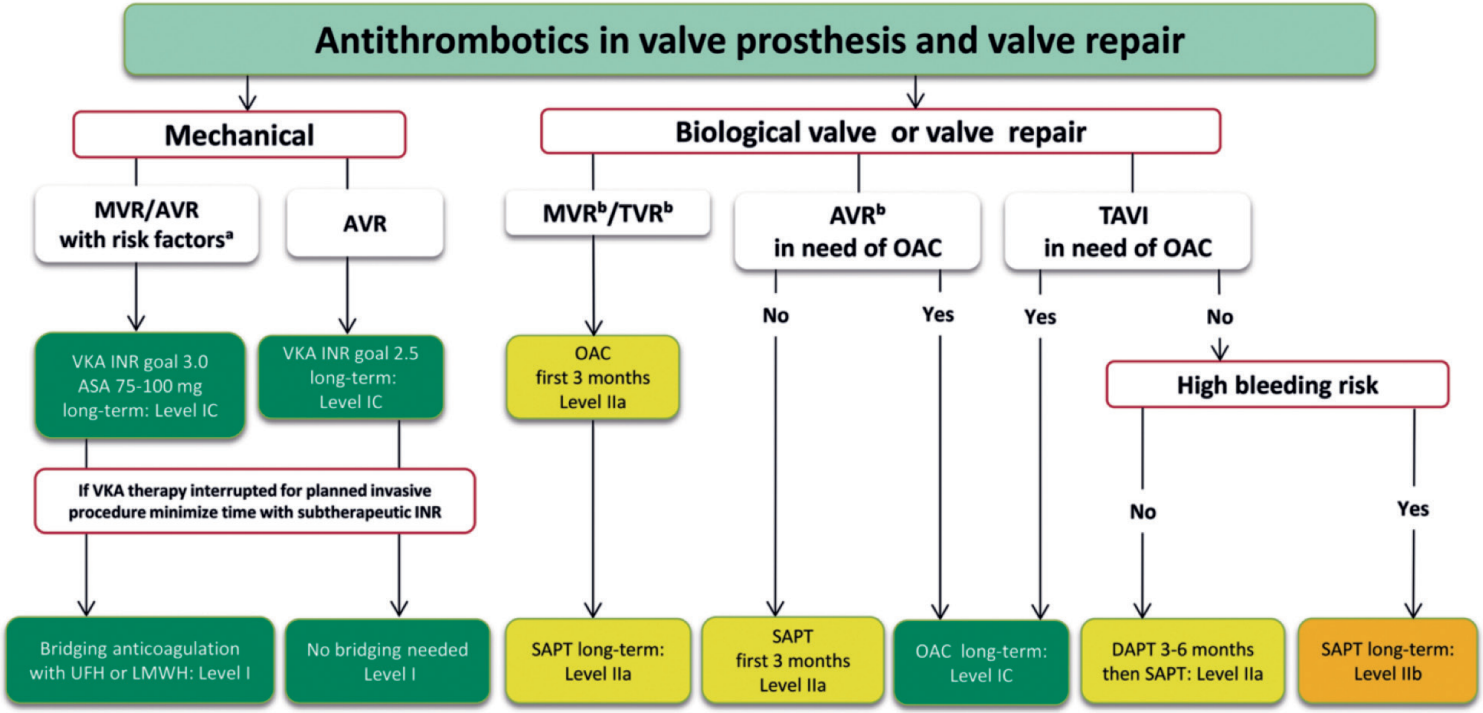


Figure 2. Proposed antithrombotic algorithm after valvular heart procedures. ASA, acetylsalicylic acid; AVR, aortic valve replacement; INR, international normalised ratio; LMWH, low molecular weight heparin; OAC, oral anticoagulants; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TAVR, transcatheter aortic-valve implantation; TVR, tricuspid valve replacement UFH, unfractionated heparin; VKA, vitamin-K antagonists. [a]Includes: atrial fibrillation, previous thromboembolic events, left ventricular dysfunction and older-generation mechanical AVR; [b]stands for replacement or repair.

PCC (FEIBA®, 30 to 50 U/kg) may be considered (79). Although FEIBA® and its high potential to overshoot thrombin generation might be more efficient in the case of life-threatening bleeding, this benefit should be balanced against an increased risk of thrombosis (80). Target concentration ranges from studies on apixaban/edoxaban are lacking. Idarucizumab has recently been approved for reversing the effect of dabigatran based on the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) trial, which demonstrated complete reversal of the anticoagulant effects within minutes (81). No outcome data are available and treatment duration, as well as monitoring, is still to be established (81). The effect of andexanet alfa in reversing the effect of FXa inhibitors has shown promising results, although clinical data are currently unavailable (82, 83).

POSTOPERTIVE ANTITHROMBOTIC AND BRIDGING

Heart valve replacement or repair increases the risk of thromboembolic complications, requiring the need for antithrombotic therapy. Scientific evidence for the best antithrombotic strategy and duration is scarce (84), resulting in a low level of evidence for most recommendations (16).

Mechanical prostheses

Patients undergoing mechanical valve implantations require lifelong treatment with VKA guided by INR (Figure 2, Table 2) (85, 86). Anticoagulant treatment with UFH and VKA is started on the first postoperative day and is maintained until INR is in the therapeutic range. However, special attention of the coagulation status and potential bleeding events is required. In the case of bleeding disorders, VKAs should be restarted whenever deemed safe and preferably within 48 hours. Of note, similarly to preoperative bridging, UFH administered by the IV route remains the only approved bridging treatment after the implantation of mechanical heart valve prostheses (87), although it has never been evaluated in a randomised trial. Off-label bridging with subcutaneous LMWH is widely implemented in hospital protocols due to its logistic and cost advantages over UFH. However, prospective open label non-randomised studies have shown subcutaneous enoxaparin to be suitable for a much higher proportion of patients within the target anticoagulation range, as compared to UFH, and provide similar or better safety. It should, therefore, be considered as an alternative bridging strategy to UFH (88, 89). Once the INR is in the adequate target range, bridging should be discontinued.

The INR target in patients with mechanical prostheses depends on certain patient characteristics (e.g. previous thrombosis, AF) and the prosthesis thrombogenicity and implantation site (e.g. aortic, mitral or tricuspid) (16). A median target INR of 2.5 (range 2.0–3.0) is consistently recommended for aortic prostheses without additional risk factors for thromboembolism (16, 90), while higher targets are recommended in patients with risk factors (e.g. AF, venous thromboembolism, hypercoagulable state, left ventricular ejection fraction (LVEF) <35%) and/or mitral and tricuspid prostheses (median target INR >3.0). Of interest in patients with mechanical heart valves, the time in the therapeutic range is better associated with safety than the target INR range (91), supporting the use of INR self-management (92-94).

The Randomized, phase II study to Evaluate the Safety and pharmacokinetics of Oral Dabigatran in patients after heart valve Replacement (RE-ALIGN) trial investigated whether dabigatran versus VKAs was safe and effective in patients with mechanical heart valves (95). The trial was prematurely stopped because of an increased risk of both thromboembolic complications and major bleeding with dabigatran. Therefore, NOACs currently have no role in any patient with mechanical heart prostheses.

In patients with concomitant atherosclerotic disease, the addition of low-dose (75–100 mg) ASA to VKAs may be considered, although the evidence is limited. Furthermore, a low dose of ASA may also be added if thromboembolism occurs despite an adequate INR. However, combined antithrombotic therapy is associated with significant increase in the bleeding risk, which carries an ominous prognosis (96). Therefore, it should be reserved for very high thromboembolic risk settings like patients with a mechanical valve and an absolute indication for DAPT (e.g. recent stent implantation or ACS), a short period (1 month) of triple therapy comprising VKA, low-dose ASA and clopidogrel may be considered (16), followed by interruption of either ASA or clopidogrel. Ticagrelor and prasugrel are not recommended in a triple therapy setting due to the safety hazard (16).

Bioprostheses

The optimal anticoagulation early after implantation of an aortic bioprosthesis surgery remains controversial. Either anticoagulation with VKA or single antiplatelet therapy (SAPT) with ASA during the first three months should be considered. A large study from the US Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database found comparable rates of death, embolic events and bleeding in patients treated with ASA alone or VKAs alone for three months after

bioprosthetic aortic valve replacement, while combined ASA and VKA therapy reduced death and embolic events but significantly increased bleeding (97). A Danish registry study showed a higher incidence of thromboembolic events and cardiovascular mortality in patients discontinuing warfarin during the first six postoperative months (98), although this cannot be directly translated into an increased risk if warfarin treatment is not initiated. A recent small RCT of 370 patients found that three-month warfarin versus ASA therapy significantly increased major bleeding while not reducing death or thromboembolic events (99). There are no data on continuing lifelong ASA after an initial three months of treatment in patients with surgical bioprostheses who do not have any other indication for ASA.

Three months of treatment with VKA is recommended in all patients with a bioprosthesis implanted in the mitral or tricuspid position.

Valve repair

It is recommended to consider oral anticoagulation with VKA during the first three months after valve-sparing aortic root surgery, and after mitral and tricuspid repair, although strong evidence is lacking. As for other indications, the risk of thromboembolic and bleeding complications must be taken into account when the antithrombotic treatment is planned.

Transchateter aortic-valve implantation

The decision for (dual) antiplatelet therapy or oral anticoagulation after TAVI is complicated due to multiple factors associated with i) a prothrombotic environment after valve implantation, ii) combined TAVI and stent implantation in 30% of patients, and iii) an elderly patient population that frequently bears comorbidities and frailty characteristics and should be considered at high risk of bleeding. DAPT remains the most widely used antithrombotic strategy after TAVI, being used in >60% of patients, while VKAs are used in <20% of patients (100). However, subclinical valve thrombosis is another challenging issue as it may occur soon after TAVI with antiplatelet treatment and may only be reversed after exposure to oral anticoagulant (OAC) therapy (101). Indeed, recent evidence demonstrates that VKA alone versus VKA plus ASA produced comparable rates of thromboembolic events and mortality while reducing bleeding events (102). Which antithrombotic regimen (e.g. antiplatelet, VKA or NOAC) is most appropriate after TAVI is currently being tested in several ongoing trials (NCT02247128, NCT02556203, NCT02664649). For the moment, there is a consensus that DAPT should be used soon after TAVI when there is no indication for OACs.

Patients who are receiving preoperative anticoagulation

In patients undergoing any cardiac surgery with a preoperative indication for OACs other than heart valve replacement or repair, the preoperative regimen of VKAs or NOACs should be reinitiated after surgery. Patients with a preoperative indication for bridging should also receive postoperative bridging, following the same scheme as for mechanical prosthetic heart valves shown in Figure 1. As opposed to VKAs, restarting NOACs after surgery should be done more cautiously due to the more immediate antithrombotic effects and the increased risk of bleeding (95).

ATRIAL FIBRILLATION

Preoperative prophylaxis

The most common arrhythmia in the postoperative period of cardiac surgery is AF, and it is associated with longer hospital stay, stroke rate, and mortality (103-105). It is also a predictor of AF occurrence years after surgery (105). Since the previous comprehensive version of the guidelines on the prevention and management of de novo atrial fibrillation after cardiac (106), numerous studies have addressed the safety and efficacy of medication to prevent postoperative AF (POAF) (17). Treatment with beta-blockers has been shown to reduce POAF (103, 107). Therefore, patients who are already taking beta-blockers should remain on treatment before and after surgery. Patients without beta-blockers may derive some benefit with a lower incidence of POAF when starting beta-blockers 2–3 days before surgery (if tolerated), and carefully up-titrated according to blood pressure and heart rate (108). Amiodarone six days preoperatively and six days postoperatively has been shown to be more effective than beta-blockers, but it is associated with more acute and long-term complications (107, 109). It may be considered in patients who are unable to tolerate beta-blockers. Studies suggest that both magnesium and fish oil may prevent POAF, but RCTs have shown conflicting evidence (110-112). Therefore, a clear recommendation for their use cannot be provided at the moment. There is currently no evidence from clinical trials to support the use of colchicine, steroids or statins to prevent POAF.

Management of postoperative atrial fibrillation

In hemodynamically unstable patients because of POAF, cardioversion and antiarrhythmic drugs to restore sinus rhythm are recommended. Amiodarone or vernakalant are both effective for restoring sinus rhythm after POAF (113, 114).

Historically, in haemodynamically stable patients, rhythm control of POAF has been the norm due to the assumption that the restoration/maintenance of sinus rhythm would be a superior strategy to rate control. More recent evidence has shown that, in asymptomatic or minimally symptomatic patients, there is no benefit to adopting a rhythm control strategy, even with amiodarone (115). However, 25% of patients in the rate control group crossed over to the rhythm control group and vice versa, limiting the ability of the trial to show a significant benefit of one strategy over the other. Therefore, in asymptomatic or minimally symptomatic patients, a rhythm control strategy should be the preferred strategy, while rate control may also be an option. For rate control, beta-blockers or diltiazem/verapamil (if beta-blockers are contraindicated) are preferred over digoxin (17, 116). The choice of drug depends on patient characteristics, including haemodynamics and LVEF. A combination of beta-blockers and digoxin may be required.

Prevention of thromboembolism in postoperative atrial fibrillation

Anticoagulation therapy is necessary for postoperative cardiac surgery patients who develop AF to avoid early stroke and mortality (117). OAC reduces postoperative mortality in patients discharged with POAF. Nevertheless, there is no clear evidence on when to start anticoagulation, and the decision has to be made based upon balancing bleeding and thromboembolic risk. Starting early with a therapeutic dosage of UFH or LMWH should be considered within 12 to 48 hours after surgery. OAC should commence 48 hours after and maintained for at least four weeks according to the CHA_2DS_2-VASc score (17, 118). Most of the evidence for anticoagulation of POAF has been obtained with VKAs. For patients with mechanical valve prostheses or moderate-to-severe mitral stenosis, VKAs are highly recommended (17). There is evidence supporting a greater benefit of NOACs over VKA in non-valvular POAF, including a bioprosthetic valve (119, 120).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) INHIBITORS

There are four classes of drugs that may be used to inhibit the renin-angiotensin system (RAAS): 1) angiotensin-converting enzyme inhibitors (ACEIs); 2) angiotensin II receptor blockers (ARBs); 3) aldosterone receptor antagonists; and 4) direct renin inhibitors (DRI). RAAS-blockers are mainly used to treat hypertension and heart failure, but may also protect against the development of nephropathy through their inherent properties, which are not only directly

related to their effects on lowering blood pressure (121, 122). Nevertheless, the use of RAAS blockers in some patients is fraught with controversy (122-125). The role of newly developed DRIs in the settings of cardiac surgical patients is uncertain, and data are currently lacking.

Preoperative discontinuation

It has been debated whether ACEIs should be discontinued before CABG (122, 123,126). The Ischemia Management with Accupril Post Bypass Graft via Inhibition of the Converting Enzyme (IMAGINE) study did not show any benefit of quinapril administration within seven days of surgery or placebo, with greater morbidity and mortality observed at three months in the quinapril group (127). However, the exact timing of the discontinuation and re-institution of the drug is poorly defined (124, 127). RAAS inhibitors, including the ARBs and ACEIs, can also increase the risk of perioperative hypotension (128) and vasodilatory shock (129), causing decreased systemic vascular resistance (SVR) (124). Therefore, the use of inotropes and vasopressors is increased and their time on ventilators and in the intensive care unit (ICU) is extended (123, 130). For these reasons, there is a consensus on discontinuing RAAS-blockers before cardiac surgery (Table 4) (122, 123, 126). In patients with preoperatively uncontrolled hypertension, long-acting ACEIs and ARBs may be switched to short-acting ACEIs. Additionally, sacubitril/valsartan-treated patients should have the same preoperative assessment like other patients treated with the RAAS inhibitors. There are currently no data on whether aldosterone receptor antagonists should be stopped or continued until surgery.

Table 4. Different types of Renin-Angiotensin-Aldosterone System Inhibitors.

	Captopril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan
Mechanism of Action	ACEI	ACEI	ACEI	ACEI	ARB	ARB
Half-life[a]	2 hours	35-38 hours	12 hours	13-17 hours	6-9 hours	6-9 hours
Frequency of administration	Twice- or thrice daily	Once- or twice-daily	Once daily	Once- or twice-daily	Once- or twice-daily	Once- or twice-daily
Maximum dose	450 mg/day	40 mg/day	40 mg/day	20 mg/day	100 mg/day	320 mg/day
Renal excretion	95%	61%	100%	60%	4%	13%
Discontinuation before non-acute surgery	12 hours	24 hours	24 hours	24 hours	24 hours	24 hours

[a]including half-life of its pharmacologically active metabolite. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Postoperative use

The ideal blood pressure goal following CABG is not well studied, but a pressure of less than 140/90 mmHg has been suggested to be optimal (131, 132). Therapy of postoperative hypertension frequently involves beta-blockers, as they also reduce the risk of AF/flutter and improve the clinical outcomes of patients with heart failure and reduced LVEF (133). ACEIs, however, should also be considered, often in addition to beta-blockers in patients with postoperative hypertension and/or a reduced LVEF (124, 131, 132). Furthermore, treatment with sacubitril/valsartan is recommended in patients who remain symptomatic with chronic heart failure (NYHA > II) and who have a reduced LVEF (< 40%) as a replacement for an ACEI to further reduce the risk of mortality and readmission (19). ARB can be used as an alternative blood pressure therapy in patients with reduced LVEF that are intolerant to ACEIs (134,135), but should rather not be used concomitantly to ACEIs due to increased rates of hypotension, hyperkalaemia and impaired kidney function, especially if aldosterone antagonists are also used (136). For other patients without hypertension or a reduced LVEF, the routine use of ACEIs is not indicated, as it may potentially lead to more adverse events (127, 137). The occurrence of LCOS in the early postoperative phase may result in a prolonged ICU stay, and a need for inotropes or vasopressors support, which is associated with ischaemia and renal complications (138).

After the early postoperative phase, RAAS-blockers have protective effects in CABG-patients with reduced LVEF and impaired kidney function (124), mainly for long-term prevention of adverse events (139). In addition to ACEIs and ARBs, aldosterone receptor antagonists may also benefit patients with chronic heart failure or a reduced LVEF. This benefit was shown in the Randomised Aldactone Evaluation Study (RALES) trial, where aldactone reduced overall mortality, heart failure symptoms and readmission due to heart failure (140). Eplerenone, another aldosterone antagonist, was subsequently shown, in the Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF), to reduce the risk of death and heart failure rehospitalisation in patients with an LVEF <35% and NYHA-class II (141). Aldosterone antagonists can be used together with beta-blockers and ACEIs in patients following CABG but should be limited to patients with reduced LVEF and NYHA-class II–IV heart failure symptoms (141-143). They should, however, be avoided in patients with kidney failure (eGFR <30 ml/min/1.73 m^2) or hyperkalaemia (>5.0 mEG/L) (143).

BETA-BLOCKERS

Preoperative beta-blockers

Current evidence recommends that patients should continue beta-blockers before elective and non-elective cardiac surgery (144-146), as doing so results in a consistent survival benefit plus a reduction in arrhythmic events in the early postoperative period (147). However, the effectiveness of catecholamine in the early postoperative period may be limited by concurrent treatment with beta-blockers until day of surgery (148). Therefore, it may be cumbersome to control patients with preoperative long-acting agents, and it should, therefore, be considered to switch to short-acting agents to limit adverse events.

The question of whether to initiate a beta-blocker in the preoperative or postoperative period is less clear (149), and such a decision should be individualised, involving weighing of the risks and benefits. As discussed in the chapter on AF, initiating beta-blockers preoperatively may be considered for the prevention of POAF. Whether beta-blockers prevent perioperative MI and mortality is a controversial topic. Studies have shown that beta-blockers are particularly beneficial in patients with a recent MI (150). Indeed, it is suggested that the benefit of beta-blockers before CABG to prevent MI and death is limited to patients with recent MI only (151). There is conflicting evidence on whether preoperative beta-blockers are beneficial in patients with reduced LVEF but without a recent MI (152). However, if beta-blockers are initiated preoperatively, careful up-titration of short-acting agents, according to blood pressure and heart rate, starting several days before surgery is recommended.

Postoperative beta-blockers

In addition to a preoperative beta-blockade in patients with reduced LVEF, continuing beta-blockers during the early postoperative phase has also been shown to significantly reduce 30-day mortality following CABG (153). Strong evidence suggests that beta-blockers reduce mortality in patients with recent MI or reduced LVEF (<35%) (154, 155). Therefore, it is crucial that beta-blockers are continued upon discharge for long-term secondary prevention in patients with a recent MI or reduced LVEF (156-158). Approved beta-blockers are metoprolol succinate, bisoprolol, nebivolol and carvedilol (19).

DYSLIPIDAEMIA

Statins

Preoperative statin therapy

Observational studies and small RCTs have suggested that initiation of preoperative statin therapy before cardiac surgery reduced mortality, POAF and acute kidney injury (AKI) (159,160). However, in the Statin Therapy in Cardiac Surgery (STICS) trial that randomised 1,922 patients undergoing elective cardiac surgery, the initiation of rosuvastatin therapy (20 mg/day) before cardiac surgery did not prevent perioperative myocardial damage or reduce the risk of POAF (161). AKI was significantly more common among patients who received rosuvastatin than among those who received a placebo (161). In another trial of patients undergoing cardiac surgery, high-dose initiation of atorvastatin on the day before surgery and continuing perioperatively compared with placebo did show a significantly higher rate of AKI in patients with chronic kidney disease (162). The trial was later prematurely terminated on the grounds of futility (163). In summary, these recent data do not support the preoperative initiation of statin therapy in statin-naïve patients undergoing cardiac surgery. No data are available on whether patients already taking statins should continue or discontinue therapy preoperatively, although in common practice statins are continued perioperatively.

Postoperative use

Intense or maximally tolerated statin therapy is recommended with a low-density lipoprotein cholesterol (LDL-C) target of <70 m/dl (1.8 mmol/L) or >50% LDL-C reduction in patients with CAD. In the Treating to New Targets (TNT) trial, which included >4,000 randomised patients, intense LDL-C lowering (to a mean of 79 mg/dl (2.05 mmol/L)), with atorvastatin 80 mg/day in patients with previous CABG, reduced major cardiovascular events by 27% and the need for repeat revascularisation by 30%, as compared with less intensive cholesterol lowering to a mean of 101 mg/dl (2.61 mmol/L) with atorvastatin 10 mg/day (164). In patients with statin intolerance during follow-up, the European Atherosclerosis Society has recently developed a scheme for statin re-exposure (165).

Non-statin lipid lowering agents

In patients after CABG surgery in whom the LDL-C target <70 mg/dl (1.8 mmol/L) is not reached despite an intense or maximally tolerated statin dose, the addition of a cholesterol absorption inhibitor, ezetimibe, should be considered. In a recent analysis of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, it was observed that patients with a prior experience

of CABG surgery who received ezetimibe plus a statin versus a statin alone had a substantial reduction in cardiovascular events during a six-year median follow-up (6).

Although no direct evidence of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use after cardiac surgery exists, the circumstantial evidence provides enough facts for its beneficial effects as well after CABG surgery (166). Patients in whom the LDL-C target <70 mg/dl (1.8 mmol/L) is not reached despite an intense or maximally tolerated statin and ezetimibe dose, the recently developed PCSK9 inhibitors have been shown to reduce cardiovascular events during follow-up in patients at high cardiovascular risk (167, 168). Therefore, the addition of PCSK9 inhibitors should be considered in selected patients.

A meta-analysis of 18 RCTs and 45.058 patients showed that fibrates, agonists of peroxisome proliferator-activated receptor-alfa, could reduce major cardiovascular events predominantly by prevention of coronary events, but with no impact on mortality (169). However, in recent studies, no additional benefit of fibrate treatment on top of statin therapy has been demonstrated (170). Bile acid sequestrants (cholestyramine, colestipol, colesevelam) reduce LDL-C by 18-25% and may be used in combination with statins (20). However, gastrointestinal adverse events and drug interactions limit their use.

ULCER PREVENTION AND STEROIDS

Ulcer prevention

Based on older studies, the incidence of upper gastrointestinal ulceration and bleeding is around 1% after cardiac surgery and is associated with significant morbidity and mortality (30–40%) (171). However, patients undergoing contemporary cardiac surgery are aggressively treated with antithrombotic medication, and the incidence may, therefore, be underestimated. The impact of gastrointestinal ulcers and bleeding may be larger due to higher comorbidities and more potent antithrombotic medication.

Studies have shown that patients continue to have gastrointestinal complications despite intraoperative H2 antagonist therapy and that more robust prophylaxis is required (172). A summary of the available evidence concluded that a proton-pump inhibitor (PPI), but not H2 (histamine) antagonist, reduced gastrointestinal complications (173). Indeed, the largest randomised trial of 210 patients

undergoing cardiac surgery randomly assigned patients to Teprenone, Ranitidine or Rabeprazole, and found that patients treated with a PPI (Rabeprazole) had a significantly lower rate of active ulcers of 4.3% compared to 21.4% and 28.6% in the patients treated with the H2 antagonist (Ranitidine) and the mucosal protector (Teprenone) respectively (174). Therefore, prophylaxis with a PPI should be considered, even though there is a concern that routine prophylaxis may increase the incidence of postoperative pneumonia (175). However, there is conflicting evidence to support this statement (176).

Steroids

The use of cardiopulmonary bypass (CPB) initiates a systemic inflammatory response, which is associated with adverse clinical outcomes such as respiratory failure, bleeding, adverse neurological function and multiple organ failure (177). Steroids attenuate this systemic inflammatory response, and thus theoretically there is a potential benefit of steroids for patients undergoing cardiac surgery with CPB, although steroids may also increase the risk of infective complications and MI.

A meta-analysis of 44 RCTs (n=3205) looking at the use of steroids in patients undergoing on-pump CABG showed that steroids reduced POAF, postoperative bleeding, and the duration of ICU stay but failed to show a reduction in mortality (178). Steroids did not increase the rate of MI or infective complications. On the basis of this analysis, the Steroids in Cardiac Surgery (SIRS) trial was conducted (179). In the trial, 7,507 patients with a EuroSCORE >5 who underwent cardiac surgery with CPB were randomised between methylprednisolone or placebo, showing no difference in the risk of 30-day mortality (4% vs. 5%, respectively) or the risk of mortality and major morbidity (24% vs. 24%, respectively). Although there was no difference in the rate of infections or delirium, there was a safety concern due to significantly higher rates of myocardial injury. The Dexamethasone for Cardiac Surgery (DECS) trial randomised nearly 4,500 patients undergoing cardiac surgery with CPB and confirmed that no benefit was found with steroids over placebo in the composite of mortality, MI, stroke, renal failure or respiratory failure (180).

In summary, the routine use of prophylactic steroids is not indicated for patients undergoing cardiac surgery. However, a subgroup analysis of the DECS trial demonstrated an interaction according to age, suggesting that patients younger than 65 years may have a benefit of the preoperative use of steroids (181). Indeed, younger patients generally have a more pronounced inflammatory response than

elderly patients, and therefore suppression of this effect with steroids could have a potential benefit. Patients on chronic steroid therapy should receive their usual preoperative dose of steroids on the day of surgery. Additional perioperative stress-dose steroids for these patients is reasonable, but not evidence-based medicine (182).

ANTIBIOTIC PROPHYLAXIS

Perioperative infections following cardiac surgery, including surgical site infections (SSIs), bloodstream infections, pneumonia and C. *difficile* colitis, dramatically affect survival, are the cause of prolonged hospitalisation or readmission, and significantly increase costs (183). Moreover, these major infections are of particular importance since they have a relatively high prevalence of nearly 5% in total cardio-surgical population (184).

Surgical antibiotic prophylaxis (SAP) before cardiac surgery is recommended to decrease the incidence of major infections. In addition to intravenous SAP administration, the gentamicin-collagen sponge has been developed to keep a high concentration of the agents in the local tissues surrounding postoperative wounds. The results from a recent meta-analysis showed significant risk reduction of sternal wound infection after implantation of gentamicin-collagen sponges (185). However, the heterogeneity among studies was large and powerful studies to confirm the benefit of additional local intervention in certain patient populations are warranted.

Dosing of surgical antibiotic prophylaxis

Rates of infection after cardiac surgery are lower in patients with higher (versus lower) antibiotic serum concentrations at the time of starting CPB, as well as at the end of surgery (186, 187). To date, because of its safety, effectiveness, and user-friendliness, SAP in cardiac surgery is routinely based on standardised doses rather than weight-based doses, which avoid the need for individual patient calculations and therefore clearly reduce the risk of dosing errors (Table 5). Nevertheless, based on limited evidence that exists for optimal dosing in obese patients (188, 189), the dose of cephalosporin should not routinely exceed the usual adult dose. For patients with renal failure, dosing should be adjusted according to the creatinine clearance.

Duration of surgical antibiotic prophylaxis

Repeat intraoperative dosing is recommended to ensure adequate serum and tissue concentrations if the duration of the procedure exceeds two half-lives of the antibiotic agent or when there is excessive intraoperative blood loss. Indeed, a randomised trial of 838 patients comparing a single-dose versus a 24-hour multiple-dose cefazolin regimen in patients undergoing cardiac surgery reported higher SSI rates with the single-dose regimen (190). A recent meta-analysis of 12 RCTs with 7,893 patients showed that SAP administered ≥24 versus <24 hours significantly reduced the risk of SSI by 38% (95% CI 13–69%, P=0.002) and the risk of deep sternal wound infections by 68% (95% CI 12–153%, P=0.01) (191). Other studies have failed to show the benefit of prolonging SAP to >48 hours (192, 193), while this does increase the risk of acquired antibiotic resistance compared with shorter prophylaxis (194-196). Therefore, based on current evidence, the optimal length of SAP in adult cardiac surgery is 24 hours and should not exceed 48 hours. Whether intermittent or continuous antibiotic administration should be preferred remains unclear, although some evidence suggests that continuous infusion may reduce postoperative infectious complications (197). For a strategy of intermittent administration, the exact timing of redosing depends on the half-life time of the antibiotic agent that is used. It should, furthermore, be adjusted for a prolonged antibiotic half-life time in patients with renal failure (198-201). Moreover, repeating SAP shortly after initiation of CPB has recently been shown to ensure adequate drug levels (201).

Choice of surgical antibiotic prophylaxis

The majority of pathogenic organisms isolated from patients with SSIs after cardiac surgery are gram-positive bacteria, which are followed by gram-negative bacteria. Only a minority of other bacteria, anaerobes, fungi and parasites have been identified (202, 203).

Particularly due to rising numbers of methicillin-resistant Staphylococcus aureus (MRSA) infections among patients undergoing cardiac surgery, the importance of eradicating intranasal Staphylococcus aureus colonisation is stressed. There is clear evidence from large RCT that intranasal mupirocin twice daily for four days prior to cardiac surgery significantly reduces SSIs in patients known to be colonised with Staphylococcus aureus (204, 205). However, for patients in whom the status of colonisation is unknown, testing for colonisation well in advance of cardiac surgery should be considered to allow the appropriate preoperative duration of mupirocin eradication treatment in colonised patients. Although this introduces logistical difficulties and has cost implications, such a strategy should

be preferred over routine mupirocin treatment in patients with an unknown colonisation status.

Table 5. Half-life time of the most used antibiotics for SAP[a].

Antibiotic Agent	Half-life time
Ampicilline	60 minutes
Ampicilline/Sulbactam	60 minutes
Amoxicilline	60 minutes
Amoxicilline/Clavulanate	60 minutes
Cefazolin	94 minutes
Cefotaxime	60 minutes
Cefotiam	45 minutes
Ceftriaxone	7–8 hours
Cefuroxime	70 minutes
Ciprofloxacin	3-5 hours
Clindamycin	2.5 hours
Gentamicin	1.5–2 hours
Imipenem	60 minutes
Levofloxacin	7–8 hours
Meropenem	60 minutes
Metronidazole	7 hours
Piperacillin	60 minutes
Piperacillin/Tazobactam	45 minutes
Tobramycin	1.5–2 hours
Vancomycin	6 hours

[a]Repeat intraoperative dosing if the duration of the procedure exceeds two half-lives of the antibiotic agent or when there is excessive intraoperative blood loss or hemodilution. SAP, surgical antibiotic prophylaxis.

For systemic antibiotic prophylaxis, numerous studies have clearly shown that antibiotic prophylaxis with first- and second-generation cephalosporins can effectively reduce the incidence of SSI and postoperative infectious complications in patients undergoing cardiac surgery (Table 6) (206-208), even though a meta-analysis showed that second-generation cephalosporins might be superior in reducing SSIs (209). In patients with a ß-lactam-allergy who cannot tolerate cephalosporins, Clindamycin or Vancomycin is sufficient for gram-positive coverage (210-213). However, up to 15% of hospitalised patients reported allergy to penicillin, but after a formal allergy evaluation, between 90-99% of these patients

are found to be able to safely underwent penicillin treatments (214). Importantly these patients are more likely to be treated with vancomycin, clindamycin and quinolones with the increased risk of developed drug-resistant infections such as vancomycin-resistant Enterococcus and Clostridium difficile (215), leading to increased mortality, morbidity and prolonged hospital stays. Therefore, implementation of hospital protocols, including preoperative skin testing may be effective therapeutic tools to reduce the rates of intra-hospital infections, lower costs of antibiotics and improve the patient's outcome (214, 216).

In patients colonised with MRSA in whom cephalosporins are insufficient, the administration of Vancomycin is recommended (217-219).

Table 6. Recommendations for the choice of SAP.

Type of procedure	Recommended agents	Alternative agents in patients with ß-lactam allergy	Strength of evidence
CABG	Cefazolin, cefuroxime	Clindamycin, Vancomycin	A
Cardiac device implantation (e.g. pacemaker)	Cefazolin, cefuroxime	Clindamycin, Vancomycin	A
Ventricular assist devices	Cefazolin, cefuroxime	Clindamycin, Vancomycin	C
Heart, lung, heart-lung transplantation	Cefazolin	Clindamycin, Vancomycin	A

CABG, coronary artery bypass grafting; SAP, surgical antibiotic prophylaxis.

Anaesthesia and postoperative analgesia

Anaesthetic agents and techniques might impact clinically relevant postoperative outcomes through pharmacological organ protective mechanisms (220, 221) and by blunting the stress response (222). Halogenated anaesthetics (Isoflurane, Desflurane and Sevoflurane) are commonly used anaesthetic drugs with hypnotic, analgesic and muscle-relaxant properties. On top of this, halogenated anaesthetics versus total intravenous anaesthetics result in additional organ protection and improvements in clinically relevant endpoints after CABG, including reduction of mortality and perioperative MI (220, 221, 223-228).

Postoperative pain following cardiac surgery still occurs frequently, both in the ICU and in the general ward (229). It is often underdiagnosed and undertreated, especially in patients who are unable to self-report pain, and an overall more than half of the operated patients report pain as the most traumatic experience of their postoperative stay (230, 231). General recommendations for pain assessment developed for general surgery and the ICU are also indicated in cardiac surgery patients. Adequate pain relief is associated with improved outcomes through a

better respiratory function (e.g. an effective cough), early mobilisation, delirium, and a reduction of cardiovascular complications, which lead to a reduced ICU stay and lower associated costs. Poorly treated pain can have long-term sequelae, which negatively impacts the quality of life and increases healthcare-related costs (232, 233).

Regional anaesthesia for perioperative pain control

Locoregional techniques (epidural, intrathecal analgesics, paravertebral block, intercostal nerve block, wound infiltration) provide excellent postoperative pain control with different documented impacts on clinically relevant outcomes (234-238).

Epidural analgesia started before surgery, and following published guidelines for epidural catheter positioning and removal (233), is also associated with a possible mortality reduction (222) and a low risk of epidural hematoma (239). Intrathecal ('Spinal') administration of morphine has been demonstrated to reduce postoperative opioid consumption and may be an alternative to epidural analgesia, as it is associated with reduced risk of epidural hematoma (234, 240). Administration of intrathecal clonidine, in addition to morphine, may provide additional benefits in terms of pain control and mechanical ventilation (MV) duration, but it may also increase the risk of hypotension (235, 236, 241).

The paravertebral block is another alternative to neuraxial techniques. Compared with epidural analgesia, the paravertebral block showed a similar analgesic efficacy and a lower incidence of minor complications in patients undergoing thoracotomy (242). However, evidence in cardiac surgery patients is very limited. In patients undergoing median sternotomy, the bilateral paravertebral block should be performed. Although this approach appears safe and is probably associated with fewer complications compared to epidural analgesia, it requires further investigation (243).

Infiltration of local anaesthetics along the sternal wound may also be effective in reducing postoperative opioid consumption (244). However, continuous infusion through a parasternal catheter has been associated with increased risk of sternal wound infection (245). A single injection may be effective but requires further investigation (246).

Postoperative pain assessment

Routine assessment of pain and its severity improves pain management, both in the ICU and on the ward, and allows the verification of the effectiveness of analgesic medications. It permits the monitoring of the response to therapy and detection of complications and side effects. Multimodal analgesia (e.g. analgesia through different techniques or drugs acting on different pathways) is more effective than analgesia, relying on a single technique in the overall surgical population, and there is no reason to doubt that this also applies to the cardiac surgical setting (233).

Several analgesic techniques and drug classes are currently available. Intravenous opioids are currently considered 'standard of care' in the management of significant postoperative pain in the ICU after cardiac surgery. In cooperative patients, patient-controlled analgesia (PCA) is superior to nurse-controlled analgesia regarding pain control (247). Several opioids are available, with no clear evidence of the superiority of one over the others. A possible exception might be remifentanil, which has shown cardioprotective effects (248) and superiority in pain control (249, 250). Use of paracetamol (acetaminophen) is safe and reduces opioid consumption (251-254), making it the best agent to manage postoperative pain after an opioid-based cardiac anaesthesia and in combination with postoperative opioids.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are still used in cardiac surgery (255) in spite of worsening of renal function in some patients. The concomitant administration of other NSAIDs can theoretically diminish the antiplatelet effects of low-dose aspirin, increasing the risk of thromboembolic effects (heart attacks and strokes) (256-261). Nevertheless, RCTs and meta-analyses have shown that the use of low-dose NSAIDs in selected patients at low risk of adverse events is effective in reducing pain and opioid consumption and may shorten mechanical ventilation time and ICU stay (262-266). A single propensity-matched study suggested a possible reduction in mortality associated with ketorolac use (267). Therefore, their use as a second-line agent in patients without contraindications may be considered. On the contrary, RCTs showed that selective cyclooxygenase-2 (COX-2) inhibitors are associated with an increase in adverse cardiovascular events and should, therefore, not be routinely administered (268, 269). Analgesic adjuvants can reduce postoperative pain if given preoperatively (gabapentine or pregabalin) or postoperatively (ketamine) (235, 270-272).

Blood glucose management

Hyperglycaemia affects over 40% of patients after cardiac surgery, due to stress and the use of inotropes (184). Controlled studies show that patients with diabetes mellitus (DM) have increased morbidity and mortality after cardiac surgery (273). Perioperative hyperglycaemia, per se, even in non-DM patients, is associated with negative outcomes after cardiac surgery. Moreover, roughly 20–30% of cardiac surgery patients have pre-existing DM (274). DM is associated with endothelial and platelet dysfunction, leading to prothrombotic states, adverse vascular events and increased infection risk. The prevalence of unrecognised DM and pre-DM in patients undergoing cardiac surgery contributes heavily to high blood glucose concentrations (BGC) in the perioperative period (274). Small increases in perioperative BGC are associated with significant increases in hospital mortality and morbidity (274, 275). Therefore, preoperative documentation of the diagnosis of diabetes and its type should be a universal practice. Patients undergoing adult cardiac surgery should have a fast glucose measurement at hospital admission and if >120 mg/dl (6.6 mmol/L) be determined to have haemoglobin A1c (HbA1c).

Preoperative and post-ICU glucose management have no solid scientific evidence and are based on expert opinion. ICU data are controversial and should be interpreted cautiously. However, there is randomised evidence that perioperative BGC control reduces the risk of mortality and adverse events in cardiac surgery (276-278). There is also evidence that blood glucose control should be started before the operation and not deferred until after surgery. The overall adequacy of BGC monitoring in the weeks before surgery, as reflected by preoperative HbA1c, is associated with a several perioperative complications including mortality, stroke, renal failure, sternal wound infections, prolonged ICU stays and readmission (279).

Perioperative hyperglycaemia is probably a marker of illness severity rather than a cause of poor outcomes (280). Indeed, the degree of hyperglycaemia is related to the level of activation of the stress response. While mild to moderate stress hyperglycaemia is protective, it is likely that severe stress hyperglycaemia may be deleterious. However, the blood glucose threshold above which stress hyperglycaemia becomes harmful is still unknown. Many observational studies have been carried out to find the most reliable approach to blood glucose levels, and a U-shaped association between mean blood glucose levels and mortality was found, with the lowest mortality observed for the 125–160 mg/dl range (281).

Importantly, evidence points towards an increased risk of hypoglycaemic events with aggressive glycaemic control and suggests that moderate control can achieve clinically relevant improvements (282-285). The GLUCO-CABG Trial showed that intensive insulin therapy to target glucose of 100 and 140 mg/dL in the ICU did not significantly reduce perioperative complications compared with the target glucose of 141 and 180 mg/dL after CABG (286). Moreover, the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed that blood glucose control below 108 mg/dL was associated with a significant increase in all-cause mortality in ICU patients, including both surgical and non-surgical patients (287). Observational studies suggest that, particularly in patients with insulin-treated DM, glucose levels below the recommended threshold of 180 mg/dl are associated with increased complications. In patients without DM and non-insulin dependent DM, higher blood glucose levels were associated with more complications than lower blood glucose levels (288, 289). Whether or not differential glucose thresholds should be stratified according to previous diabetic status requires further large prospective randomised studies.

There is high variability in methods of and indications for insulin therapy, management of non-insulin agents and blood glucose monitoring among glucose management guidelines issued by several professional organisations due to controversial findings and the lack of high-quality studies (290). A multidisciplinary 'diabetes team' should be in charge of continuous IV insulin infusion protocols, treatment algorithms for the transition to subcutaneous insulin after discharge from the ICU, nutritional requirements and the reintroduction of oral anti-diabetics, using hospitalisation as a 'window of opportunity' for patient education, treatment selection and dose adjustment (Figure 3).

Before hospital discharge, the patients with a diagnosis of DM or pre-DM should have an endocrinology consultation and dietary counselling. Post discharge, plasma glucose and HbA1c levels should be followed up regularly, with appropriate adjustments made in insulin and oral hypoglycaemic therapies with the aim of keeping HbA1c <7%.

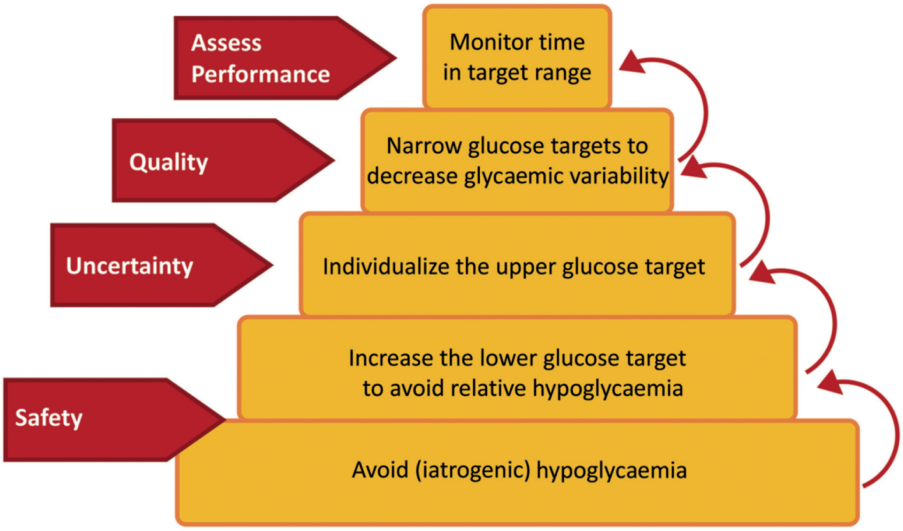


Figure 3. A recommended bottom-to-top stepwise strategy to implement perioperative blood glucose control (modified from Preiser et al. (282)).

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Chapter 17

Mixing 'apples and oranges' in meta-analytic studies: dangerous or delicious?

Milojevic M, Sousa-Uva M, Durko AP, Head SJ.

Eur J Cardiothorac Surg. 2018;53:1294-1298.

TO THE EDITOR:

Sá *et al.* (1) observed no significant difference regarding the risk of perioperative myocardial infarction (MI) if the administration of acetylsalicylic acid (ASA) was stopped or continued in patients before undergoing coronary artery bypass graft (CABG) surgery. Compared with a similar meta-analysis reported by Hastings *et al*. (2) in 2015, only the results from the more recently released ATACAS trial were added to the analysis. However, we have a major concern regarding the inclusion criteria of this meta-analysis.

First, the appropriateness for the inclusion criteria of a study is questionable. The variation in design across studies is high, i.e. from the continuation of ASA until the day of surgery to the initiation of ASA in na¨ıve patients on the day of surgery. For example, in the aspirin and tranexamic acid for coronary artery surgery (ATACAS) study (3), which consisted of approximately 50% of all patients included in this meta-analysis, patients were only eligible if they were not taking or stopped taking aspirin at least 4 days before surgery and were randomized to receive 100 mg of aspirin or placebo on the day of surgery. Therefore, patients who continued aspirin were not included in the trial, which is highly misleading with regard to the title of the article.

Moreover, if we wanted to test whether a single dose of aspirin on the day of surgery would reduce ischaemic events in patients who discontinued aspirin for at least 4 days before surgery, the given 100 mg dose would only result in partial platelet inhibition. When stopping the administration of aspirin, full platelet function recovery is observed after 96 h (4), and a (re)loading dose of at least 160 mg would be required to sufficiently inhibit platelet function (5). Second, since other included studies fulfilled the criteria of full platelet inhibition based on the dose of administered ASA, this meta-analysis mixes the results of patients with total and partial platelet inhibition, with potentially misleading consequences. The authors also performed a sensitivity analysis excluding the ATACAS study: the reported finding was still non-significant about the effect of continued ASA on the reduction in perioperative MI (risk ratio 0.62, 95% confidence interval 0.37–1.05; $P = 0.074$). This is particularly interesting in the light of a recent meta-analysis published by Hastings and colleagues from Melbourne (2). This study—neither cited nor discussed by the authors—demonstrated a significant reduction in perioperative MI with continued ASA (odds ratio 0.56, 95% confidence interval 0.33–0.96; $P = 0.03$)—with the exact same studies included as in the sensitivity analysis performed by Sa *et al.* (1). These results seem to depend on the effect measure that

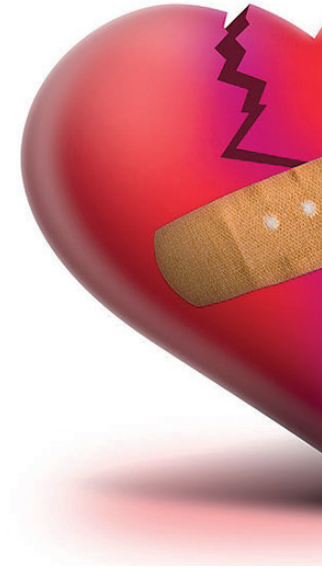
is chosen and that by itself introduces a dilemma on how strong the evidence is. However, borderline *P*-values cannot be considered as a strong argument either for or against an intervention, and the risk–benefit ratio of thrombotic risk versus bleeding risk should be considered in treatment decision-making.

The recently published EACTS Guidelines on perioperative medication in adult cardiac surgery recommends that 'in patients on ASA who need to undergo CABG surgery, continuing ASA throughout the preoperative period should be considered (Class IIa, Level of Evidence C)' (6). This is mainly based on the meta-analysis by Hasting *et al.* (2), where the use of ASA resulted in a 44% reduction in perioperative MI with an acceptable increase in the total chest blood drainage (mean + 168 ml).

On the basis of these arguments, we do not believe that the results of the ATACAS study and other studies that randomized patients to either ASA or placebo on the day of surgery are appropriate in a meta-analysis aiming to answer the question of whether to stop or continue ASA before CABG. From the perspective of recently published several clinical guidelines, this meta-analysis is confusing and may be potentially misleading due to its strong conclusions. On the basis of the risk–benefit ratio, we believe that ASA should be continued throughout the perioperative period in patients awaiting CABG who are not at a high bleeding risk.

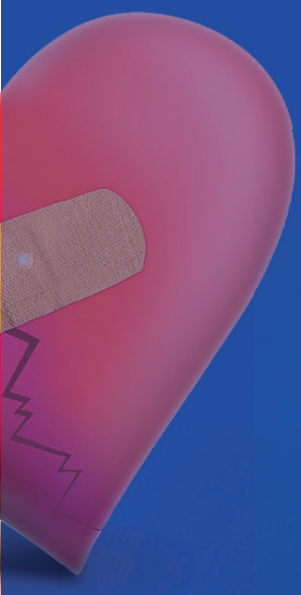
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Part 4

Summary and Discussion



Chapter 18

Summary

Chapter 1 is a general introduction to this thesis. This chapter gives an overview of the epidemiology and current trends in myocardial revascularization in Europe. Although both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are used in patients with left main (LM) disease and/or multivessel disease, the optimal patient selection and individualized medication strategies are crucial to ensure improved outcomes. Rigorously developed evidence-based recommendations in clinical guidelines can improve decision-making and quality of health-care. The studies in this thesis should inform clinicians about specifically choosing revascularization strategies for patients with coronary artery disease. The aims and outline of this thesis are described in **chapter 2.**

Part 1.

Current Practice in Bypass Surgery

Chapter 3 describes the outcome and life expectancy of the first venous CABG procedures during 40 years of follow-up. The 10-, 20-, 30and 40-year survival for the 1041 patients who underwent CABG between 1971 and 1980 was 77%, 39%, 14% and 4%, respectively. Average life expectancy was 18 years while repeat revascularization was performed in 36% of patients. Factors associated with decreased late survival were the age at operation, diabetes mellitus (DM), multivessel disease and left ventricular ejection fraction under 50%. However, over the last four decades, surgical techniques have improved, increasing its safety and efficacy while at the same time reducing invasiveness and re-intervention demands. The proper use of surgical techniques is most closely linked to the revascularization success or failure. A critical evaluation of contemporary indications, techniques, and outcomes of bypass surgery are discussed in **Chapter 4.** This review suggests that, despite its improvements, several techniques for CABG surgery can be adopted more widely to further improve outcomes: use of intraoperative graft flow assessment, epiaortic scanning, more use of arterial conduits, and hybrid revascularization.

To steer the choice of the most optimal technique, clinical practice guidelines are one of the most valuable tools. One of the major advances has been a class IC recommendation for the multidisciplinary “Heart Team” decision-making process in the North American and European guidelines for revascularization. Evidence to support the Heart Team is scarce, and some clinicians fear that the

requirement of a Heart Team discussion can delay treatments and be unsafe for patients. **Chapter 5** provides evidence that real-world Heart Team meetings are feasible and safe in evaluating coronary artery disease complexity and additional comorbidities along with patient's preferences to guide the most appropriate revascularization strategy. Approximately 90% of patients received treatment within 6 weeks, as recommended by the 2014 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization. Delay was caused by the need for additional diagnostic tests to be performed, showing that logistics can be further improved.

Part 2.

Bypass Surgery versus Stenting

Several multicenter randomized clinical trials (RCTs) have examined the clinical effects of PCI versus CABG across patients with multivessel and/or LM disease. One of these trials was the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial; a large randomized multicenter study comparing PCI with first-generation drug-eluting stents (DES) (TAXUS™ Express™, Boston Scientific) to CABG for patients with three-vessel and/or LM disease. A significant contribution of the SYNTAX trial was the development of the SYNTAX score, which has become a unique tool to score the complexity of coronary artery disease (CAD) and to help guide decision-making between PCI and CABG.

The RCTs that have been performed used various composite endpoints with a varying clinical impact to boost the statistical power, but no study has been adequately powered to examine the mortality differences as the primary outcome. **Chapter 6** provides an individual patient-data pooled analysis of 11518 patients from 11 RCTs, which showed a significantly higher 5-year mortality rate after PCI than after CABG in patients with multivessel disease, especially in those with diabetes and higher coronary complexity according to the core laboratory SYNTAX scores. Furthermore, in patients with LM disease, no difference in mortality rate was seen between two treatment groups. In **Chapter 7**, the specific cause of mortality was examined based on data from the SYNTAX trial, demonstrating that cardiac death due to spontaneous myocardial infarction (MI) was markedly higher after PCI with TAXUS compared to CABG at 5-year of follow-up.

Stroke following PCI and CABG, although rare, can be a devastating complication, associated with high rates of mortality and reduced health-related quality of life. In **Chapter 8**, we found, among 11518 patients randomized to CABG or PCI with stents, that PCI was associated with significantly lower 30-day stroke rates compared to CABG (0.4% versus 1.1%, respectively), but no difference was found between two treatment groups beyond 30-day after the procedures. Comparing CABG with PCI, diabetes had a significant effect on the occurrence of stroke during 5 years of follow-up (2.6% versus 4.9%, P for Interaction = 0.004). The reason for the higher rates of stroke after CABG may be multifactorial, including the use of antifibrinolytics to reduce the risk of bleeding after surgery. **Chapter 9** is a letter to the editor that stresses the importance of the correct intraoperative dose of antifibrinolytics-tranexamic acid (TXA) agent to prevent bleeding complications after CABG, but also highlights that the routine use of TXA may influence the perioperative stroke occurrence in CABG.

In **chapter 10**, additional analyses from the SYNTAX trial were conducted to explore the impact of repeat revascularization on the 5-year clinical outcome. Rates of repeat revascularization are higher after PCI compared with CABG at all-time points. Our study reports that at 5-year follow-up, repeat revascularization rates were significantly higher after PCI compared to CABG (13.7% versus 25.9%, P<0.001), showing a significant correlation between any repeat revascularization after an initial PCI procedure and increase in the incidence of serious adverse events. Moreover, long-term results have also demonstrated a significantly higher need for multiple repeat revascularization after an initial PCI than after CABG (9.0% versus 2.8%, P=0.022; respectively). Independent predictors of repeat revascularization were diabetes, incomplete revascularization, the number of overlapping stents and absence of antiplatelet therapy among patients randomized to PCI while the treatment in the United States and the use of off-pump technique were reliable predictors of repeat revascularization in the CABG group.

Apart from the individual endpoints of mortality, myocardial infarction, stroke, and repeat revascularization, clinical trials often use composite endpoints to increase the statistical power of the analyses. Individual endpoints in composites are weighted equally, while the different individual components have evident varying impacts on long-term prognosis. Therefore, several novel approaches to assess the results of composite endpoints have been introduced. In **chapter 11,** a win ratio approach is applied on the SYNTAX trial to provide additional clinical insights into the results of the primary composite endpoint

of mortality, stroke, MI or repeat revascularization, also evaluating strengths and weaknesses of alternative methods for the analysis of composite endpoints. This study demonstrates that the critical advantage of CABG over multivessel PCI is the reduction of hard clinical endpoints such as mortality and MI. Moreover, this approach is readily applicable to analyze composite endpoints with multiple distinct events, while maintaining the integrity of the study results.

Multiple factors can influence treatment decision-making. Patients with chronic kidney disease (CKD) and/or diabetes have a high prevalence of CAD and high risk of cardiovascular mortality. Whether the use of PCI or CABG would improve patient survival in patients with these associated diseases remains uncertain due to limited data from randomized comparisons and conflicting data from observational studies. To address this knowledge gap, the effect of CKD on 5-year outcome after PCI and CABG in the SYNTAX trial has been investigated in **chapter 12.** This subgroup analysis shows that CABG appears to be the favorable revascularization strategy over PCI, mainly supporting the more significant use of CABG among diabetic patients complicated by CKD. A randomized study of 1905 patients with LM disease, enrolled in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial compared CABG with second-generation DES. Patients with diabetes had a significantly higher rate of the 3-year composite primary endpoint of death, stroke or MI (12.9% versus 20.0%, P<0.001) (**chapter 13**). However, there was no difference in the primary endpoint between PCI and CABG in diabetic patients (20.7% versus 19.3%, P=0.87) and non-diabetic patients (12.9% versus 12.9%, P=0.89), suggesting that in selected diabetic patients with LM, PCI may be a reasonable treatment approach beyond CABG.

The globalization of clinical trials has emerged as a new phenomenon describing the movement of trial location to lower-income countries to decrease costs and accelerate recruitment of trial participants. One of the major concerns is that the imbalance between the quality of care, patient health levels, treatment choice, and hospital infrastructures may influence the overall generalization of the trial results. **Chapter 14** focuses on the influence of practice patterns on outcomes in specific countries within the SYNTAX trial. We found that baseline characteristics of included patients and clinical practice patterns are substantially different between participating countries, resulting in a significant difference in clinical outcomes, for which specific treatment recommendations were provided. Furthermore, relevant aspects for future trial design are discussed.

Part 3.

Improving Outcomes in Cardiac Surgery

Advances in the whole spectrum of hospital care have resulted in significant improvements of in-hospital outcomes in patients undergoing CABG. However, CAD is a chronic progressive process that requires intensive postoperative medication therapy to slow down the progression of the disease and reduce the risks of future cardiovascular events. Clinical guidelines are developed to help in decision-making by providing recommendations that are supported by the best available evidence. Along with increasing awareness of clinical outcomes between different treatment modalities, clinical trials can provide valuable information about the use of guideline-recommended medical therapy (GDMT) in daily practice. In **chapter 15**, based on an individual patient-data analysis of 7085 patients from 5 RCTs, we studied the compliance with GDMT after myocardial revascularization. The pooled analysis shows the suboptimal use of GDMT after CABG and significant correlation between the optimal use of medications and risks of adverse clinical outcomes at 5 years of follow-up. Moreover, in **chapter 16,** we provide the evidence-based recommendations for perioperative medical therapies in adult cardiac surgery. **Chapter 17** is a letter to the editor that discusses the evidence used to answer the question regarding stopping or continuing acetylsalicylic acid (ASA) until the day of CABG. The main finding of this meta-analysis was opposite to our clinical guideline recommendations. Therefore, methodological comments on the inclusion and exclusion criteria for given meta-analysis and the most important trials in this field are put into perspective to substantiate the recommendations in our treatment guidelines.

Chapter 19

General Discussion

This thesis aimed to identify patients with stable coronary disease who, based on projected outcomes, should be preferentially selected for CABG or PCI, but also to provide considerations for clinical decision-making and designs of future clinical trials. In this chapter, the main findings will be put into broader perspective, highlighting the implications for current clinical practice. Moreover, future directions for research are presented.

Current Practice in Bypass Surgery (Part 1)

Coronary artery bypass grafting (CABG) remains the most common operation performed by cardiac surgeons today (1). The procedure has significantly evolved over the past 50 years into a technique that is safe and efficient (2). Despite an increasingly higher risk profile of patients, advances in surgical techniques as well as in the whole spectrum of patient care are associated with a continuous reduction in postoperative complications even in contemporary practice. Fifty years ago, the use of the saphenous vein grafts helped to establish CABG as a standard of care for patients with refractory angina, but its tendency for progressive failure has caused a high incidence of repeat revascularization early after initial venous CABG. In a review of the literature on contemporary indications, practice patterns, and outcomes of CABG, we found that modern techniques can markedly improve the durability of myocardial revascularization with less need for repeat revascularization. Recent procedural achievements such as appropriate conduit selection, no-touch procedures, epiaortic scanning, intraoperative graft assessment, minimally invasive procedures, robotic-assisted surgery will undoubtedly bring less post-operative complications, particularly stroke, improving the life-expectancy and health-related quality of life. On the other hand, despite these proven benefits, low adoption rates of the essential surgical techniques in many surgical centers is deeply worrying. It is remarkable that use of single internal mammary artery (IMA) that is considered the gold-standard conduit in CABG for more than 30 years (3), remains far away from being widely accepted (4). With this knowledge as a reality, the hospital and national quality improvement programs should play a vital role in bridging the gaps between scientific evidence and clinical practice, to ensure patients access to efficient and high-quality care (5).

Another crucial element to improve the outcomes of patients with CAD is patient selection on the basis of specific treatments that are individualized to the unique characteristics of the particular patient. It is well acknowledged that a variety of risk factors are known to influence postprocedural complications and long-term outcomes. According to the latest European and American revascularization

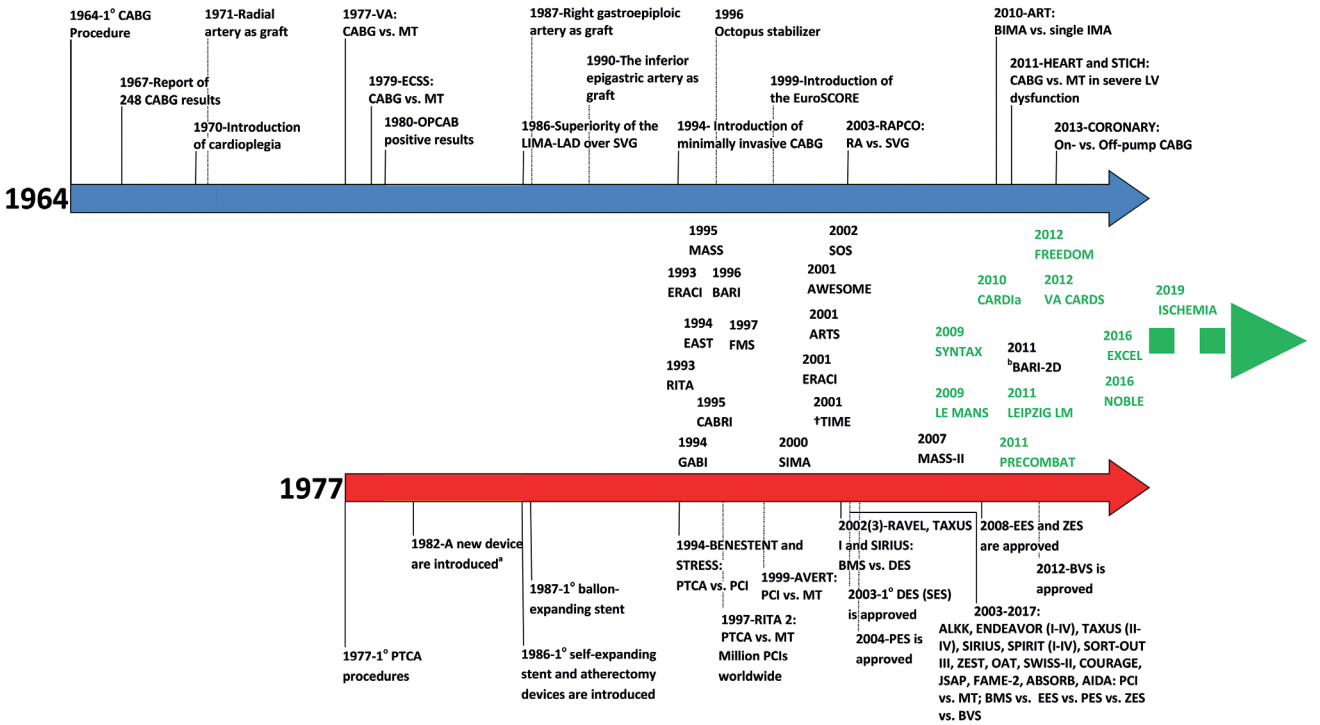


Figure. Timeline of developments and randomized comparisons in myocardial revascularization treatment over the past five decades.

guidelines, the cornerstone for decision-making involves the formation of Heart Teams, which includes a multidisciplinary team consisting of a clinical/non-invasive cardiologist, interventional cardiologist, and cardiac surgeon, with other specialists as needed (6, 7). The purpose of the Heart Team concept is to identify the most appropriate treatment for the particular patient and help patients and their family to reach the best treatment choice. These Heart Teams have a class I but the level of evidence C recommendation. There is no evidence from studies to support Heart Teams, and many clinics, therefore, lack a formal Heart Team discussion. One of the limitations may be an increase in waiting times for patients to undergo a procedure. We demonstrated that a real-world Heart Team approach is a feasible strategy for the management of patients with stable coronary artery disease (CAD) while it does not compromise the waiting time for treatment. Moreover, the final treatment decisions in the majority of cases were adherent to the recommendations of the guidelines, suggesting that this team approach can promote transparency in decision-making and minimize physician-related bias.

Bypass Surgery versus Stenting (Part 2)

Improvements in outcomes of CABG surgery have been paralleled if not exceeded by improvements in outcomes after percutaneous coronary intervention (PCI). As a result, numerous randomized clinical trials (RCTs) have been performed to compare the safety and efficacy of PCI versus CABG in patients with CAD (Figure). While PCI is now an established first-line treatment for patients with acute indications and those with a relatively simple CAD, it remains unclear whether CABG or PCI should be preferred in patients with more complex disease as defined by multivessel coronary disease or involvement of the left main (LM) stem.

Several trials evaluated the effects of CABG versus PCI with balloon angioplasty, while later trials compared CABG with PCI with bare metal stent (BMS) among patients with multivessel disease. Over a median follow-up of 5.9 years, the pooled analysis of individual data on 7812 patients from these 10 RCTs shows no difference between CABG and PCI in the rates of death (8.4% versus 10.0%, P=0.12), but the composite outcome of death, MI or repeat revascularization was significantly lower after CABG than after PCI (20.1% versus 36.4%, P<0.001) (8). The superiority of CABG over PCI was established in patients with diabetes (12.3% versus 20.0%,) while mortality was similar between groups in non-diabetes patients (7.6% versus 8.1%) (P for interaction=0.014). With the introduction of drug-eluting stents (DES) and dual antiplatelet therapy (DAPT) as the standard of care (9, 10), ischaemic complications and the need for repeat revascularization have been reduced after

PCI. As a result, PCI is increasingly considered to be a safe and effective approach for patients with multivessel and/or LM disease and diabetes (DM). These improvements have led to further comparisons between PCI with first-generation DES and CABG in several trials. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial is one of the most contemporary and influential trials, comparing PCI with first-generation DES (TAXUS™ Express™, Boston Scientific) to CABG in 1800 patients with three-vessel and/or LM disease, who were deemed eligible for treatment by both CABG or PCI. The main results showed that CABG (with the use of at least one arterial graft) is superior to PCI in term of the primary composite endpoint of all-cause death, stroke, myocardial infarction (MI), and repeat revascularization with first-generation DES, mainly due to the reduction of spontaneous MI and the need for repeat revascularization (11). The results of other clinical trials have reported similar outcomes as the SYNTAX trial. CABG reduced the rate of spontaneous MI and need for repeat revascularization while PCI was associated with lower rates of stroke. Second-generation DES with use of more effective antiplatelet agents were developed to further improve the outcomes after PCI but failed to demonstrate comparability to CABG among patients with multivessel disease enrolled in the Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease (BEST) trial. Nevertheless, available evidence from the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial that compared CABG with PCI using newer-generation DES among patients with LM disease suggested similar outcomes for the composite of death or stroke, or MI up to 3.5 years of follow-up, but need for repeat revascularization remain significantly higher after PCI. These results have not been confirmed in the Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial.

Since all individual RCTs were underpowered to detect a difference in mortality rates, a pooled analysis of individual data of 11518 patients from 11 RCTs was performed to examine the risk of mortality following CABG versus PCI with stents. The absolute difference in mortality at 5-year follow-up was small but significant (CABG 9.2% versus PCI 11.2%, P=0.004). While the investigated studies are different with regard to the inclusion criteria such as the anatomical complexity of CAD, we also found the advantage of CABG over PCI in patients with multivessel disease and diabetes, but not in patients with LM disease and those with multivessel disease without diabetes. Moreover, the death rate of PCI versus CABG was significantly increased with higher SYNTAX scores (linear trend test, P=0.011), confirming that the anatomical complexity assessed by SYNTAX score can be a

useful tool in selecting the proper revascularization strategy (12). The majority of patients with LM disease have in recent years been treated in a background context of consistent progress in contemporary PCI practice, including safer and more effective DES and better adherence to secondary prevention medical therapy, suggesting that PCI for LM disease has become a viable option in selected cases with the appropriate angiographic and clinical settings.

A post-hoc analysis of the SYNTAX trial aimed to determine the specific cause of mortality at 5-year follow-up. Although the Surgical Treatment for Ischemic Heart Failure (STICH) trial has shown a significant benefit of CABG over medical therapy in the reduction of sudden cardiac mortality or MI-related mortality events (13), the findings of the SYNTAX trial for the first time indicate that CABG-treated patients were at significantly lower risk of cardiac mortality than those managed with PCI. Furthermore, CABG particularly reduces the incidence of cardiac mortality events as a consequence of spontaneous MI. This reduction was most significant in patients with more complex lesion complexity (diabetes, three-vessel disease, or a SYNTAX score >=33) which strengthens the previous finding that was found in the pooled analysis of the individual patient data from 11 RCTs.

Beyond mortality, it is also important to consider other major cardiovascular events that can significantly impact the quality of life following myocardial revascularization, particularly stroke. The occurrence of stroke was infrequent in randomized trials and therefore insufficient to detect clinically meaningful differences between PCI and CABG (14, 15). In the pooled dataset of 11 RCTs, PCI retained an advantage over CABG regarding significantly lower 30-day and 5-year rates of stroke, though the rates of stroke were similar between 31 days and 5 years. The mechanisms underlying the increased risk of periprocedural stroke with surgery are likely multifactorial including polyvascular disease, surgical techniques, routine use of prophylactic procoagulant agents and cerebral hypoperfusion during cardiopulmonary bypass. We found that the higher risk of stroke after CABG compared to PCI was restricted to patients with diabetes and multivessel disease, which may be associated with a higher burden of atherosclerotic disease not only in the coronary arteries but also in the aorta and carotid arteries. Different strategies can be used to combat emboli and their resultant stroke after CABG. These include aortic no-touch techniques, epiaortic scanning, monitoring of cerebral oximetry for early detection and treatment of cerebral hypoxia, avoiding the use of antifibrinolytic agents in patients at high risk of recurrent stroke, and the more aggressive start of postoperative anticoagulation in patients who have developed atrial fibrillation.

One of the main findings of the SYNTAX trial was that CABG compared with PCI, provides markedly less need for repeat revascularization (13.7% versus 25.9%, *P*<0.0001). Although in PCI with newer-generation DES, the incidence of in-stent restenosis and need for repeat revascularization is lower compared to PCI with first-generation stents (16), several studies performed after the SYNTAX trial have also reported higher rates of repeat revascularization (17). Repeat revascularization is often considered to be a benign endpoint in RCTs. However, no studies have provided an analysis to provide insights into incidence, characteristics, and outcomes of repeat revascularization. Therefore, we performed an in-depth investigation of repeat revascularization at 5-year follow-up in the SYNTAX trial. Importantly, we found that repeat revascularization was an independent predictor of hard clinical endpoints in the PCI group, driving the difference between CABG and PCI in the overall results. On the other hand, similar outcomes between PCI and CABG patients who did not undergo repeat revascularization suggests that careful patient selection by Heart Team is essential to minimize risks of adverse events caused by the inappropriate choice of revascularization procedure (18). In addition to a previously published study that identified predictors of repeat revascularization after PCI with newer-generation DES (19), our results add significantly to the current body of evidence. The main results emphasized the importance of diabetes and incomplete revascularization after PCI and off-pump surgery after CABG as predictors of future repeat revascularization. Furthermore, as shown in our results, the importance of secondary prevention is essential to improving outcomes in this regard.

The SYNTAX trial was unique in the inclusion of patients with mild-to-moderate chronic kidney disease (CKD). In the most recent European guideline, it remains unclear whether PCI or CABG should be preferred in patients with CKD (7). Thus, we provided the comparative effectiveness of the two revascularization strategies in patients with CKD (Chapter 12). We found a profound negative impact of CKD compared to patients with normal kidney function on 5-year survival following both PCI (26.7% versus 10.8%, P<0.001, respectively) and CABG (21.2% versus 10.6%, P=0.005, respectively). We also found that concomitant diabetes was the most critical determinant of long-term survival after PCI (40.9% versus 17.7%, P=0.004). Additionally, deficiencies in the use of recommended medications after both CABG and PCI are noted. The benefit of secondary prevention therapies is crucial in patients with CKD to derive maximum benefit from myocardial revascularization (20, 21). Experience from numerous clinical trials in the field of cardiovascular medicine has shown a strong link between subgroup analyses and the future findings of dedicated RCTs if the results are interpreted correctly.

Although the SYNTAX trial has found that PCI was inferior to CABG for the primary outcome at 5 years (11), a secondary analysis suggested that subgroup of patients with LM disease and low-to-intermediate SYNTAX scores (0-32) had similar results with PCI and CABG (22). This hypothesis has been further tested by the EXCEL trial that compared PCI with newer-generation DES (XIENCE Family Stent System, Abbott Vascular) in 1905 patients with significant LM disease eligible for either PCI or CABG and a SYNTAX score <=32 (23). The primary composite endpoint of all-cause death, stroke or MI in this trial indicated that PCI with DES was noninferior to CABG for clinical and functional results at 3 years (24, 25). In a pre-specified subgroup analysis of the EXCEL trial we found that compared to non-diabetic patients, diabetic patients had higher 3-year rates of the composite primary endpoint, including higher rates of all-cause death, MI, and ischemia-driven revascularization, again reinforcing the fact that diabetes is one of the most critical determinants of long-term outcomes after myocardial revascularization irrespective of the location of coronary lesion. In line with the findings from the pooled analysis of individual patient data from the PRECOMBAT and the SYNTAX trials (26), patients who underwent PCI had a similar rate of the 3-year primary composite endpoint of death, stroke or MI compared to those who underwent CABG, in both diabetes and non-diabetes-treated patients. However, similarly to the findings from the FREEDOM trial (27), we found the significant difference in all-cause mortality between PCI and CABG at 3 years in diabetic patients (13.6% versus 8.0%, P=0.046), but not in non-diabetic patients (5.5% versus 5.0%, P=0.71). Longer-term follow-up results are necessary to provide insights into the durability of PCI in LM patients with diabetes. These observations from subgroup analyses reinforce the need for experienced Heart Team to recommend PCI to achieve optimal outcomes in selected patients, but also assist clinicians in improving adherence to medication in patients with CKD. After all, long-term medication management mainly depends on the treating clinician who prescribes secondary prevention at discharge, rather than on primary care physicians, who will be reluctant to assume such responsibility themselves.

An essential feature to reduce sample size, lower costs and the time for enrollment in clinical trials, is the use of composite endpoints. A growing number of clinical trials use composite outcomes, in which mortality and nonfatal events are combined into a single endpoint to compare treatment effects. Ideally, the events in composite outcomes need to be of high clinical importance and share similar severity. To date, clinical trials of myocardial revascularization were only powered to detect differences in the composite outcomes that incorporated a combination of three to six events with various clinical effects. These composite

outcomes may prove to be one of the leading **challenges** in the interpretation of trial results, particularly if the components are of widely differing importance for patients such as mortality and the need for repeat revascularization with PCI (28). Therefore, the conventional reporting of composite outcomes has an inherent limitation, and clinicians usually need to **develop rigorou**s habits of critical thinking between risks and benefits during the interpretation of trial results. To overcome these limitations, several alternative methods are designed to assess the composite outcomes, including the win ratio methodology (29, 30). Based on clinical impact, the win ratio approach was applied to the results of the SYNTAX trial, accounting for the severity of the individual components within the primary composite endpoint. We showed that the win ratio methodology was able to analyze the different components of the composite endpoint and also could adequately discriminate clinical outcomes between the two treatments. Although this analysis was "hypothesis-generating" only, our findings strengthen the results in favor of CABG, confirming that mortality and spontaneous MI occurred more frequently in patients treated with PCI. The win ratio analysis has also been applied and assessed within the TRILOGY ACS trial (31). In line with our findings, the authors concluded that the use of win ratio approach is a valuable alternative to a traditional time-to-event analysis especially in studies where multiple non-fatal events are more common. We propose that future clinical trials should adopt this approach to provide additional insights into trial results, but also to maximize efficacy through the use of smaller sample sizes, and therefore, to decrease the cost of research. If it is not used as the primary method for analyzing clinical trial results, using the win ratio for sensitivity analyses will improve interpretation of results.

The previously mentioned clinical trials in the field of myocardial revascularization obtained their main results based on the collaboration between medical institutions from many different countries. Since the early 2000s, the rapid expansion and integration of industry-supported clinical trials at sites in developing countries can be attributed to several factors, including the lower cost of local investigators and treating patients, deregulation of bureaucratic and/or ethical standards, and accelerating patient recruitment (32). The main advantage of conducting clinical trials on a global scale is building supportive relationships among clinicians, but also answering clinical questions that are applicable worldwide and could serve as a basis for harmonization of clinical practice. At the same time, the results from cardiovascular trials showed differences between participating countries for many reasons (33), including the disparities in health care systems, medical infrastructure, local practice patterns,

and socioeconomic status of patients (34). In Chapter 14, we analyzed the treatment differences between participating countries and its impact on the final results of the SYNTAX trial. A significant finding was that patient characteristics, clinical patterns, medication regimens and outcomes were significantly different across investigated countries. In short, meaningful clinical differences in CABG techniques that may affect the outcomes such as the use of the single or bilateral IMAs, total arterial revascularization, and off-pump CABG were noted. Furthermore, substantial differences were observed in PCI-treated patients including the number of implanted stents and the use of DAPT at discharge. The discrepancy emphasizes the importance of country-level analyses as prespecified in the design of future trials. In addition, the rise of this information during local, national, and international meetings and its translation to clinical practice would contribute to the standardization of myocardial revascularization.

Improving Outcomes in Cardiac Surgery (Part 3)

Although in-hospital mortality rates have decreased in recent years as a consequence of tremendous progress achieved in perioperative patient care, the incidence of post-discharge adverse events remains high (35.36). Several studies have established that early cardiac rehabilitation with lifestyle modification and lifelong optimized medication therapies are paramount for improved survival and better quality of life (37). In line with these data, our studies have established the importance of using secondary prevention therapies as a fundamental approach in reducing the incidence of cardiovascular events. Based on individual data from 5 landmark RCTs of myocardial revascularization, a unique analysis of compliance with guideline-directed medical therapy (GDMT) after myocardial revascularization was conducted, including a total of 7085 patients (Chapter 16). The pooled data showed poor compliance with GDMT (any antiplatelet agent, beta-blocker, and statin) of 54% at discharge that has declined to 51% at 5 years of follow-up after CABG. Adherence to GDMT was consistently lower in CABG than in PCI patients at all-time points while our findings suggest a high correlation between low compliance rates and adverse clinical outcomes. The misunderstanding that CABG is a curative treatment for CAD is undoubtedly a relevant factor affecting the long-term consequences. Coronary artery disease has a progressive lifelong course that requires continued and permanent management. Based on our results, discharge of patients without optimal medication therapy reduces medication adherence in the years after CABG, although optimizing medication adherence is the fundamental factor in reducing adverse events. Therefore, dedicated clinical practice guidelines with a primary focus on the pharmacological agents that are used for primary and secondary

prevention in patients undergoing adult cardiac surgery are required to guide physicians on how to optimize medication use (Chapter 17). These projects brought together a multidisciplinary group of specialists including cardiac surgeons, cardiologists, anesthesiologists and clinical epidemiologists in a joint task force to systematically review and grade a large body of evidence. The goal was to develop evidence-based, patient-centered, clinical practice recommendations that are easy to adopt and useful in daily practice. Clear recommendations were provided on antiplatelet and anticoagulation therapies, different modalities of antihypertensive treatment, optimal glycaemic control, and lipid-lowering therapies as essential agents to prevent further cardiovascular events. However, if guidelines are to be effective, their dissemination and implementation need to be actively pursued. Several strategies must be combined for widespread implementation of clinical guidelines: i) development of short summaries 'pocket guidelines', ii) enrollment of clinical leaders from different countries in the development process to promote coherence, iii) use of professional journal and the media for promotion, iii) use of the professional platforms, iv) presentation and discussion during meetings, workshops or seminars, and v) offering feedback and recommendations on compliance. The task force members responsible for guidelines development should also identify barriers to a broader guideline acceptance and work as a team to overcome implementation barriers. In chapter 18, we express our concerns about the methodological aspects used in the meta-analysis of clinical outcomes associated with stopping or continuing acetylsalicylic acid (ASA) before CABG. The authors use inappropriate inclusion criteria to evaluate the efficacy and safety of keeping ASA until the day of CABG, and there was substantial variation in the design of studies. Importantly, the results and definite conclusion of this meta-analysis are potentially hazardous and can generate resistance among clinicians to implement useful recommendations from the recently published guidelines (38, 39). Especially for these reasons, a task force that includes a methodologist is responsible for providing clinical practice guidelines, to ensure that evidence to support recommendations is summarized and interpreted correctly. In summary, continuous development and regular update of clinical practice guidelines in contemporary healthcare as well as their implantation and critical appraisal of the recommendations must be one of the ultimate goals of academic societies.

CONCLUSIONS

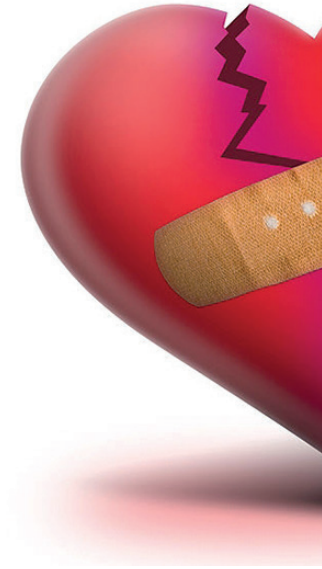
The clinical goals in the care of each patient with stable CAD are to ensure the selection of the most appropriate treatment, using the best evidence to guide procedural techniques and to modify risk factors that can impact survival and health-related quality of life. In this thesis, developments in surgical procedures, post-procedural therapies, and the most important determinants of outcomes after surgical and catheter-based myocardial revascularization are provided, thereby aiding patients and their clinicians to make the most appropriate revascularization strategy based on an individualized risk-benefit ratio. With the increasing number of clinical studies and rigorously developed clinical guidelines, a future-directed intention is needed to ensure the implementation of continuous improvement programs to increase the use of evidence-based practice in the hospital and outpatient settings to enhance the quality and safety of patient care.

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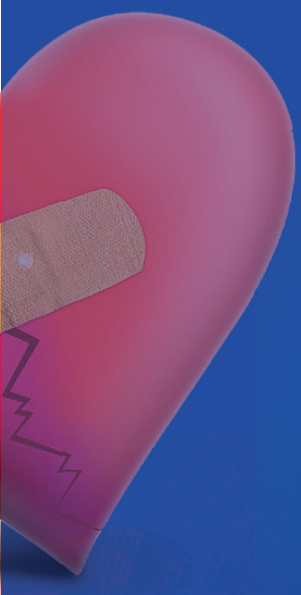
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Postscript



Chapter 20

Nederlandstalige Samenvatting

Hoofdstuk 1 is een algemene introductie van dit proefschrift. Dit hoofdstuk geeft een overzicht van de epidemiologie en de huidige ontwikkelingen op het gebied van myocard revascularisatie in Europa. Ondanks dat zowel percutane coronaire interventie (PCI) als coronaire bypass chirurgie (CABG) worden toegepast in patiënten met coronaire hoofdstam en/of meervats-coronairlijden, zijn de optimale patiëntselectie en individuele medicatie strategieën cruciaal om verbeteringen in klinische uitkomsten te kunnen bereiken. Zorgvuldig ontwikkelde aanbevelingen, gebaseerd op het beste beschikbare medisch-wetenschappelijk bewijs, samengevat in klinische richtlijnen kunnen de besluitvorming en de kwaliteit van de gezondheidszorg verbeteren. De studies in dit proefschrift dienen clinici te informeren welke specifieke revascularisatie strategie gekozen dient te worden in patiënten met coronair vaatlijden. De doelstellingen en de opzet van dit proefschrift worden beschreven in **Hoofdstuk 2**.

Deel 1.

Huidig Beleid in Coronaire Bypass Chirurgie

Hoofdstuk 3 beschrijft de uitkomsten en levensverwachtingen van de eerste veneuze CABG procedure gedurende 40-jaar follow-up. De 10-, 20-, 30en 40-jaar overleving van de 1041 patiënten die CABG hebben ondergaan tussen 1971 en 1980 was 77%, 39%, 14% en 4%, respectievelijk. De gemiddelde levensverwachting was 18 jaar, herhaalde revascularisatie werd uitgevoerd in 36% van de patiënten. Factoren die geassocieerd zijn met een afgenomen late overleving zijn: leeftijd ten tijde van operatie, diabetes mellitus (DM), meervats-coronairlijden en een linker ventrikel ejectie fractie (LVEF) lager dan 50%. De chirurgische technieken zijn in de afgelopen vier decennia verbeterd, waardoor de veiligheid en effectiviteit zijn toegenomen. Tegelijkertijd zijn de mate van invasiviteit en de noodzaak tot re-interventies afgenomen. Het adequaat toepassen van de chirurgische technieken is het nauwst gecorreleerd met succes of het falen van revascularisatie. Een kritische evaluatie van de hedendaagse indicaties, technieken en uitkomsten van coronaire bypass chirurgie wordt besproken in **Hoofdstuk 4**. Dit review suggereert dat, ondanks verbeteringen, verschillende technieken voor CABG meer wijdverspreid toegepast kunnen worden om uitkomsten verder te verbeteren, zoals het gebruik van “intra-operative graft flow assesment”, epi-aortaal scannen, toename in gebruik van arteriële conduits, en hybride revascularisatie.

Klinische richtlijnen zijn één van de meest waardevolle instrumenten om de integratie van de optimale technieken te bevorderen en daarmee behandelingen te sturen. Een van de belangrijkste vooruitgangen zijn de publicaties van Noord-Amerikaanse en Europese richtlijnen voor myocard revascularisatie, waarbij "Hart Team" besluitvorming als een klasse I C aanbeveling is opgenomen. Bewijs ter ondersteuning van een Hart-Team is schaars en sommige clinici vrezen vertragingen in het behandeltraject met onveilige situaties voor patiënten als gevolg. **Hoofdstuk 5** toont aan dat "real-world" Hart-Team besluitvorming haalbaar en veilig is voor de evaluatie van de complexiteit van coronair vaatlijden van patiënten en eventuele comorbiditeiten. Samen met de voorkeur van de patiënt leidt dit tot de meeste geschikte strategie voor revascularisatie. Ongeveer 90% van de patiënten onderging revascularisatie binnen 6 weken, wat overeenkomt met de aanbeveling van de myocard revascularisatie richtlijn uit 2014 van de Europese Vereniging voor Cardiologie (ESC) en de Europese Vereniging voor Cardio-Thoracale Chirurgie (EACTS). Vertragingen in het behandeltraject werden veroorzaakt door de behoefte aan aanvullende diagnostiek, wat aantoont dat de logistiek verder verbeterd kan worden.

Deel 2.

Bypass Chirurgie versus Stenten

Meerdere gerandomiseerde klinische studies (RCT's) hebben de klinische effecten van PCI versus CABG onderzocht in patiënten met meervats-coronairlijden en/of hoofdstam coronair lijden. Een van deze studies is de "the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) studie"; een grote gerandomiseerde multicenter studie die PCI met een eerste-generatie medicijn-afgevende stent (TAXUS™ Express™, Boston Scientific) vergeleek met CABG in patiënten met drievats-coronair lijden en/of hoofdstam coronair lijden. De ontwikkeling van de SYNTAX score, een uniek instrument om de complexiteit van coronair vaatlijden te scoren en daarmee sturing te geven aan de keus tussen PCI en CABG, was een significante bijdrage van de SYNTAX studie.

De RCT's die zijn uitgevoerd, gebruikten verschillende samengestelde eindpunten met verschillende klinische impact om daarmee de statistische kracht te vergroten. Echter, geen enkele studie was krachtig genoeg om significante mortaliteitsverschillen als primair eindpunt aan te tonen. **Hoofdstuk 6** beschrijft

een samengestelde patiënt-data analyse van 11.518 patiënten uit 11 RCT's,. Deze studie toonde een significant hogere 5-jaars mortaliteit na PCI in vergelijk met CABG in patiënten met meervats-coronairlijden, met name bij patiënten met diabetes mellitus en hogere coronaire complexiteit volgens de SYNTAX score. In patiënten met hoofdstam coronair lijden werd geen verschil gezien in mortaliteit tussen de twee behandelingsstrategieën. In **Hoofdstuk 7** werd de specifieke doodsoorzaak onderzocht middels data uit de SYNTAX studie. Deze studie toonde aan dat, na 5 jaar follow-up, cardiale dood door een mycoardinfarct aanzienlijk hoger was bij patiënten die PCI met TAXUS hebben ondergaan vergeleken met patiënten die CABG hebben ondergaan.

Een beroerte na PCI en CABG, kan, ondanks dat dit zelden voorkomt, een desastreuze complicatie zijn welke geassocieerd is met hoge mortaliteit en een afgenomen kwaliteit van leven. In **Hoofdstuk 8**, toonden wij aan dat in 11.518 patiënten welke gerandomiseerd waren naar CABG of PCI met medicatie-afgevende stents, PCI geassocieerd is met een signifcant lager aantal beroertes in de eerste 30-dagen na behandeling vergeleken met CABG (0.4% versus 1.1%, respectievelijk). Echter werd er geen verschil gevonden in beroerte aantallen tussen de twee behandelingen na de eerste 30 dagen. Diabetes had een significant effect op het voorkomen van een beroerte tijdens 5 jaar follow-up wanneer PCI met CABG werd vergeleken (2.6% versus 4.9%, P voor Interactie = 0.004). De reden voor dit hoger aantal beroertes na CABG zou multifactorieel kunnen zijn, inclusief het routinematig gebruik van antifibrinolytica welke het risico op bloeding na chirurgie verlagen. **Hoofdstuk 9** is een "letter to the editor" waarin het belang wordt onderstreept van de juiste intraoperatieve dosering van "antifibrinolytische-tranexaminezuur (TXA)" om bloedingscomplicaties na CABG te voorkomen. Tevens wordt benadrukt dat het routinematig gebruik van TXA het risico op beroerte na CABG kan beïnvloeden.

In **Hoofdstuk 10** zijn aanvullende analyses van de SYNTAX studie uitgevoerd om de gevolgen van herhaaldelijke revascularisatie op de 5-jaars klinische uitkomsten te bepalen. Het aantal herhaaldelijke revascularisaties is hoger na PCI vergeleken met CABG op alle tijdspunten. Onze studie toonde aan dat, na 5-jaar follow-up, het aantal herhaaldelijke revascularisaties significant hoger was na PCI vergeleken met CABG (25.9% versus 13.7%, P<0.001). Tevens was er een significante correlatie tussen herhaaldelijke revascularisaties na initiële PCI en een toegenomen incidentie van ernstige bijwerkingen. Lange-termijn uitkomsten hebben aangetoond dat er een significant hogere noodzaak was voor herhaaldelijke revascularisatie na de initiële PCI behandeling vergeleken met CABG (9.0% versus

2.8%, P=0.022; respectievelijk). Onafhankelijke voorspellers voor herhaaldelijke revascularisatie zijn diabetes mellitus, incomplete revascularisatie, het aantal overlappende stents en de afwezigheid van plaatjes-aggregatie remmers onder patiënten welke gerandomiseerd waren voor PCI. Behandeling in de Verenigde Staten van Amerika en het gebruik van een "off-pump" chirurgische techniek zijn betrouwbare voorspellers voor herhaaldelijke revascularisatie na CABG.

Afgezien van de individuele eindpunten zoals mortaliteit, myocard infarct (MI), beroerte en herhaaldelijke revascularisatie, gebruiken klinische studies vaak samengestelde uitkomsten om de statische kracht van de analyses te verbeteren. Individuele eindpunten in samengestelde eindpunten wegen even zwaar, terwijl verschillende individuele eindpunten duidelijk verschillende impact hebben op de lange-termijn prognose. Daarom zijn er meerdere nieuwe statistische benaderingen geïntroduceerd om deze samengestelde eindpunten te onderzoeken. In **Hoofdstuk 11** is de statistische "win ratio" benadering op de data van de SYNTAX studie toegepast om aanvullende klinische inzichten te verschaffen in de primair samengestelde uitkomst van mortaliteit, beroerte, MI en herhaaldelijke revascularisatie, waarbij ook de sterke en zwakke punten van alternatieve statische methode ten behoeve van de analyse van samengestelde eindpunten worden beoordeeld. Deze studie laat een betere uitkomst van CABG ten opzichte van PCI zien, waarneembaar in een duidelijke afname van klinische eindpunten zoals mortaliteit en MI. Bovendien is deze methode gemakkelijk toepasbaar om samengestelde eindpunten te analyseren met meerdere afzonderlijke gebeurtenissen, terwijl de integriteit van de studieresultaten wordt gewaarborgd.

Meerdere factoren kunnen invloed hebben op besluitvorming omtrent de behandeling. Er is een hogere prevalentie van coronair vaatlijden en een verhoogd risico op cardiale dood onder patiënten met chronische nierziekte en/of diabetes mellitus. Of het gebruik van PCI of CABG de overleving van dergelijke patiënten verbetert blijft onduidelijk vanwege de beperkt beschikbare data uit gerandomiseerde studies en tegenstrijdig bewijs uit observationele studies. Om deze kloof in klinische kennis te overbruggen, is het gevolg van chronische nierziekte op 5-jaars uitkomsten na PCI en CABG in de SYNTAX studie onderzocht in **Hoofdstuk 12**. Deze subgroep-analyse toont aan dat CABG de gewenste revascularisatie strategie blijkt te zijn ten opzichte van PCI, met name in patiënten met diabetes waarbij chronische nierziekte als complicatie is opgetreden. De gerandomiseerde studie onderzocht 1905 patiënten met hoofdstam coronair lijden, die geïncludeerd waren in de "Evaluation of XIENCE versus Coronary

Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)" studie, welke PCI (met tweede generatie medicatie-afgevende stents) vergeleek met CABG. Deze studie toonde aan dat patiënten met diabetes, vergeleken met patiënten zonder diabetes, een significant hogere proportie van het samengesteld eindpunt (overlijden, beroerte en MI) hadden (20.0% versus 12.9%, P<0.001, respectievelijk) (**Hoofdstuk 13**). Echter, de propotie samengesteld eindpunt bleek gelijk te zijn na behandeling middels PCI en CABG in patiënten met diabetes mellitus (20.7% versus 19.3%, P=0.87) en patiënten zonder diabetes mellitus (12.9% versus 12.9%, P=0.89). Dit suggereert dat PCI, in geselecteerde patiënten met diabetes mellitus en hoofdstam coronair lijden, een haalbaar behandelingsalternatief is voor CABG.

De globalisering van klinische trials heeft zich ontwikkeld als nieuwe modaliteit en beschrijft de verplaatsing van klinische trials naar landen met lager inkomens om aldaar kosten te besparen en inclusie van studie-patiënten te versnellen. Een van de grootste zorgen is dat de onevenwichtigheid tussen de kwaliteit van de zorg, de gezondheid van de patiënt, de behandelkeuze en de ziekenhuisinfrastructuur de algehele generalisatie van de onderzoeksresultaten kan beïnvloeden. **Hoofdstuk 14** richt zich op de invloed van de unieke manier van werken in specifieke landen op de klinische uitkomsten in de SYNTAX studie. Hierbij ontdekten wij dat zowel de karakteristieken van patiënten in de SYNTAX studie, als de unieke manier van werken substantieel verschilt tussen de deelnemende landen. Dit resulteert in een significant verschil in klinische uitkomsten, waarvoor specifieke behandel-aanbevelingen zijn aanbevolen. Tevens worden deze verschillen in het licht van toekomstige studieprotocollen bediscussieerd.

Deel 3.

Verbeteren van Uitkomsten in Hartchirurgie

Vooruitgang in het gehele spectrum van de gezondheidszorg heeft geleid tot significante verbeteringen in de klinische uitkomsten van patiënten die een CABG hebben ondergaan ten tijde van hun ziekenhuisopname. Echter, coronair vaatlijden is een chronisch progressieve ziekte die intensieve postoperatieve medicatie vereist om progressie van de ziekte te vertragen en het risico op toekomstige cardiovasculaire aandoeningen te verminderen. Klinische richtlijnen zijn ontwikkeld om medici te ondersteunen in het besluitvormingsproces door aanbevelingen te doen die worden ondersteund door het beste beschikbare

wetenschappelijk bewijs. Naast het toenemend besef over de verschillende klinische uitkomsten tussen verschillende behandelstrategieën kunnen klinische onderzoeken tevens waardevolle informatie verschaffen over het praktijkgebruik van de aanbevelingen uit klinische richtlijnen in de dagelijkse medische zorg. In **Hoofdstuk 15**, gebaseerd op een individuele patiëntendatabase-analyse van 7085 patiënten uit 5 RCT's, hebben wij de therapietrouw van de aanbevolen gezondheidszorg uit de klinische richtlijnen na myocard revascularisatie onderzocht. Deze analyse toont het suboptimaal gebruik van de door richtlijnen geadviseerde medische therapie na CABG aan en de significante correlatie tussen suboptimale medicatie van patiënten na chirurgie en het risico op ongunstige klinische uitkomsten na 5 jaar follow-up. In **Hoofdstuk 16** presenteren wij de op wetenschappelijk onderzoek gebaseerde aanbevelingen omtrent de perioperatieve medicamenteuze zorg voor volwassen hartchirurgie. **Hoofdstuk 17** is een "letter to the editor" welke het bewijs betreffende staking of continuatie van acetylsalicylzuur (ASA) in de preoperatieve dagen voorafgaand aan bypass chirurgie. De belangrijkste bevinding van deze meta-analyse was in tegenspraak met wat de klinische richtlijn aanbeveelt. Daarom worden de methodologische aspecten omtrent de inen exclusiecriteria van de uitgevoerde meta-analyse samen met de belangrijkste studies in dit gebied in perspectief geplaatst om aanbevelingen in de klinische richtlijnen verder te ondersteunen.

Chapter 21

PhD-Portfolio

Name PhD student:	Milan Milojevic
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Promotor:	Prof.dr. A.P. Kappetein
Copromotor:	Dr. S.J. Head

Academic Education

2013-2014 Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands

2007-2013 Doctor of Medicine, Faculty of Medicine, University of Belgrade, Serbia

Training	Year	ECTS
Master of Science in Clinical Epidemiology, NIHES, Rotterdam, The Netherlands	2013-2014	70
General courses		
Study Design	2013	4.3
Biostatistical Methods I: Basic Principles	2013	5.7
Clinial Epidemiology	2013	5.7
Methodological Topics in Epidemiological Research	2013	1.4
Biostatistical Methods II: Classical Regression Models	2013	4.3
Principles of Research in Medicine	2013	0.7
Clinical Decision Analysis	2013	0.7
Methods of Public Health Research	2013	0.7
Health Economics	2013	0.7
Markers and Prognostic Research	2013	0.7
The Practice of Epidemiological Analysis	2013	0.7
Advanced courses		
Epidemiology of Infectious Diseases	2014	1.4
Women Health	2014	0.9
Decision Making in Medicine	2014	1.0
Planning and Evaluation of Screening	2014	1.4
Quality of Life Measurement	2014	0.9
From Problem to Solution in Public Health	2014	1.1
Public Health in Low and Middle Income Countries	2014	3.0

Skill courses		
English Language	2013	1.4
Introduction to Medical Writing	2014	1.1
Courses for the Quantitative Researcher	2014	1.4
Academic courses		
Research Integrity	2016	0.3
Presentations		
European Association of Cardio-Thoracic Surgery (Milan, Italy)	2014	1.2
Transcatheter Cardiovascular Therapeutics (San Francisco CA, USA)	2015	1.2
European Association of Cardio-Thoracic Surgery (Barcelona, Spain)	2016	3.6
Transcatheter Cardiovascular Therapeutics (Washington DC, USA)	2016	2.4
European Society of Cardiology (Barcelona, Spain)	2017	1.2
European Association of Cardio-Thoracic Surgery (Vienna, Austria)	2017	4.8
European Association of Cardio-Thoracic Surgery (Milan, Austria)	2018	3.6
Conferences		
European Association of Cardio-Thoracic Surgery (Milan, Italy)	2014	1.2
Transcatheter Cardiovascular Therapeutics (San Francisco CA, USA)	2015	1.2
European Association of Cardiothoracic Anaesthesiology (Basel, Switzerland)	2016	0.6
European Association of Cardio-Thoracic Surgery (Barcelona, Spain)	2016	1.2
Transcatheter Cardiovascular Therapeutics (Washington DC, USA)	2016	1.2
Biomechanics in Vascular Biology and CV Disease (Rotterdam, The Netherlands)	2017	0.6
European Society of Cardiology (Barcelona, Spain)	2017	1.2
European Association of Cardio-Thoracic Surgery (Vienna, Austria)	2017	1.2
Dutch-Belgian Meeting (Antwerp, Belgium)	2017	0.6
Leipzig-Dallas Meeting (Leipzig, Germany)	2017	0.6
Society of Thoracic Surgeons (Fort Lauderdale FL, USA)	2018	1.2
Michigan Society of Thoracic and Cardiovascular Surgeons (Crystal Moun. MI, USA)	2018	0.9
European Association of Cardio-Thoracic Surgery (Milan, Italy)	2018	1.2
Transcatheter Cardiovascular Therapeutics (San Diego CA, USA)	2018	1.2
Society of Thoracic Surgeons Critical Care Conference (Washington DC, USA)	2018	0.9
Society of Thoracic Surgeons (San Diego CA, USA)	2019	1.2
Michigan Society of Thoracic and Cardiovascular Surgeons (Troy. MI, USA)	2019	0.6

In-depth courses		
Molecular Biology in Cardiovascular Research (Rotterdam)	2016	1.5
Cardiac Function and Adaptation (Papendal)	2016	2.0
Seminars and meetings		
Coeur PhD day (Rotterdam)	2016	0.3
Right Ventricular Failure (Rotterdam)	2016	0.3
Patient Oriented Reaserch: design, conduct and analysis (Rotterdam)	2016	0.3
Research in subarachnoid hemorrhage and intracranial aneurysms (Rotterdam)	2016	0.3
Discoveries in Atrial Fibrillation Pathophysiology (Rotterdam)	2016	0.3
Local scientific meetings of Dept. of Cardio-Thoracic Surgery (Rotterdam)	2016-2018	3.0
Local scientific meetings of Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (Ann Arbor, MI, USA)	2018	2.0
Teaching		
Supervising students and clinical researchers	2016-2018	2.0
Academic position		
Member of the EACTS Committee for Practice Guidelines	2017-present	
Peer reviewer international scientific journals		
Perfusion	2017-present	
European Journal of Cardio-Thoracic Surgery	2017-present	
European Heart Journal	2018-present	
Interactive CardioVascular and Thoracic Surgery	2018-present	
British Medical Journal	2018-present	
EuroIntervention	2018-present	
Editorial Board Member		
Interactive CardioVascular and Thoracic Surgery	2019-present	

Chapter 22

List of publications

1. **Milojevic M**, Head SJ, Parasca CA, Serruys PW, Mohr FW, Morice MC, Michael MJ, Stahle E, Feldman TE, Dawkins KD, Colombo A, Kappetein AP, Holmes DR Jr. Causes of Death Following PCI Versus CABG in Complex CAD: 5-Year Follow-Up of SYNTAX. *J Am Coll Cardiol.* 2016;67:42-55.

2. **Milojevic M,** Head SJ, Holmes DR Jr. Incomplete Revascularization in PCI and CABG: When Two Plus Two Does Not Make Four. *J Am Coll Cardiol.* 2016;68:878-879. Authors' reply.

3. Parasca CA, Head SJ, **Milojevic M**, Mack MJ, Serruys PW, Morice MC, Mohr FW, Feldman TE, Colombo A, Dawkins KD, Holmes DR Jr, Kappetein AP. Incidence, Characteristics, Predictors, and Outcomes of Repeat Revascularization After Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting: The SYNTAX Trial at 5 Years. *JACC Cardiovasc Interv.* 2016;9:2493-2507.

4. Sarris GE, Balmer C, Bonou P, Comas JV, da Cruz E, di Chiara L, di Donato RM, Fragata J, Jokinen TE, Kirvassilis G, Lytrivi I, **Milojevic M**, Sharland G, Siepe M, Stein J, Büchel EV, Vouhé PR. Clinical guidelines for the management of patients with transposition of the great arteries with an intact ventricular septum. *Eur J Cardiothorac Surg.* 2017;51:e1-e32.

5. Sarris GE, Balmer C, Bonou P, Comas JV, da Cruz E, di Chiara L, di Donato RM, Fragata J, Jokinen TE, Kirvassilis G, Lytrivi I, **Milojevic M**, Sharland G, Siepe M, Stein J, Büchel EV, Vouhé PR. Clinical guidelines for the management of patients with transposition of the great arteries with an intact ventricular septum. *Cardiol Young.* 2017;27:530-569.

6. **Milojevic M**, Head SJ, Andrinopoulou ER, Serruys PW, Mohr FW, Tijssen JG, Kappetein AP. Hierarchical testing of composite endpoints: applying the win ratio to percutaneous coronary intervention versus coronary artery bypass grafting in the SYNTAX trial. *EuroIntervention.* 2017;13:106-114.

7. **Milojevic M**, Kappetein AP, Head SJ. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med*. Letter to the editor. 2017;376:1892.

8. **Milojevic M**, Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD, Holmes DR Jr, Serruys PW, Kappetein AP. Influence of practice patterns on outcome among countries enrolled in the SYNTAX trial: 5-year results between percutaneous coronary intervention and coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2017;52:445-453.

9. Head SJ, **Milojevic M**, Taggart DP, Puskas JD. Current Practice of State-of-the-Art Surgical Coronary Revascularization. *Circulation.* 2017;136:1331-1345.

10. Pagano D, **Milojevic M,** Meesters MI, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Boer C. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg.* 2018;53:79-111.

11. Boer C, Meesters MI, **Milojevic M**, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Pagano D. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J. Cardiothorac Vasc Anesth.* 2018;32:88-120.

12. Sousa-Uva M, Head SJ, **Milojevic M,** Collet JP, Landoni G, Castella M, Dunning J, Gudbjartsson T, Linker N, Sandoval E, Thielmann M, Jeppsson A, Landmesser U. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg.* 2018;53:5-33.

13. **Milojevic M,** Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD, Holmes DR Jr, Serruys PW, Kappetein AP. The impact of chronic kidney disease on outcomes following percutaneous coronary interventions versus coronary artery bypass grafting in patients with complex coronary artery disease: 5-year follow-up of the SYNTAX trial. *EuroIntervention.* 2018;14:102-111.

14. **Milojevic M,** Thuijs DJFM, Head SJ, Domingues CT, Bekker MWA, Zijlstra F, Daemen J, de Jaegere PPT, Kappetein AP, van Domburg RT, Bogers AJJC. Life-long clinical outcome after the first invasive coronary artery procedures: 40-year follow-up after coronary artery bypass grafting and percutaneous transluminal coronary intervention in Rotterdam. *Interact Cardiovasc Thorac Surg.* 2019; In press

15. Head SJ, **Milojevic M**, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Mäkikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Stroke Rates Following Surgical Versus Percutaneous Coronary Revascularization. *J Am Coll Cardiol.* 2018;72:386-398.

16. Head SJ, **Milojevic M**, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Mäkikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet.* 2018;391:939-948.

17. **Milojevic M**, Serruys PW, Sabik JF, Kandzari DE, Schampaert E, van Boven AJ, Horkay F, Ungi I, Mansour S, Banning A, Taggart DP, Sabaté M, Gershlick A, Bochenek A, Pomar J, Lembo N, Noiseux N, Puskas JD, Kosmidou I, Mehran R, Ben-Yehuda O, Généreux P, Pocock SJ, Simonton CA, Stone GW, Kappetain AP. Bypass Surgery or Stenting for Left Main Coronary Artery Disease in Patients with Diabetes." *J Am Coll Cardiol.* 2019;73:1616-1628.

18. **Milojevic M,** Sousa-Uva M, Durko AP, Head SJ. Mixing 'apples and oranges' in meta-analytic studies: dangerous or delicious? *Eur J Cardiothorac Surg.* 2018;53:1294-1298.

19. Giustino G, Mehran R, Serruys PW, Sabik JF 3rd, **Milojevic M**, Simonton CA, Puskas JD, Kandzari DE, Morice MC, Taggart DP, Gershlick AH, Généreux P, Zhang Z, McAndrew T, Redfors B, Ragosta M 3rd, Kron IL, Dressler O, Leon MB, Pocock SJ, Ben-Yehuda O, Kappetein AP, Stone GW. Left Main Revascularization With PCI or CABG in Patients With Chronic Kidney Disease: EXCEL Trial. *J Am Coll Cardiol.* 2018;72:754-765.

20. Pinho-Gomes AC, Azevedo L, Ahn JM, Park SJ, Hamza TH, Farkouh ME, Serruys PW, **Milojevic M**, Kappetein AP, Stone GW, Lamy A, Fuster V, Taggart DP. Compliance with guideline-directed medical therapy in contemporary trials of coronary revascularization. *J Am Coll Cardiol.* 2018;71:591-602.

21. Durko AP, Osnabrugge RL, van Mieghem NM, **Milojevic M**, Mylotte D, Nkomo VT, Kappetein AP. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. *Eur Heart J*. 2018;39:2635-2642.

22. Sousa-Uva M, **Milojevic M,** Head SJ, Jeppsson A. The 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery and patient blood management. *Eur J Cardiothorac Surg*. Invited commentary. 2018;53:1-2.

23. Domingues CT, **Milojevic M**, Thuijs DJFM, van Mieghem NM, Daemen J, van Domburg RT, Kappetein AP, Head SJ. Heart Team decision-making for 1000 consecutive cases of coronary artery disease. *Interact Cardiovasc Thorac Surg*. 2019; 28:206-213

24. **Milojevic M,** Head SJ, Kappetein AP**.** Influences of the healthcare policy on the outcomes parameters of myocardial revascularization procedures as opposed to geographical differences. *Eur J Cardiothorac Surg*. 2018;54:196-197. Authors' reply.

25. **Milojevic M,** Boer C, Pagano D. Are we underestimating the value of minimal invasive extracorporeal circuits in blood conservation? *Eur J Cardiothorac Surg*. 2018;54:200. Authors' reply.

26. Thuijs DJFM, **Milojevic M**, Head SJ. Doubling up on antiplatelet therapy after CABG: changing practice ASAP after DACAB? J Thorac Dis. 2018; In press.

27. **Milojevic M,** Pisano A, Sousa-Uva M, Landoni G. Perioperative Medication Management in Adult Cardiac Surgery: The 2017 European Association for Cardio-Thoracic Surgery Guidelines. J. Cardiothorac Vasc Anesth. Invited commentary 2018; In press.

28. Freemantle N, **Milojevic M**, Lim S, Fremes S, Pagano D. 32nd EACTS Annual Meeting clinical trials update: ART, IMPAG, MITRA-FR and COAPT. Eur J Cardiothorac Surg. 2019;55:186-190.

29. Head SJ, Papageorgiou G, **Milojevic M,** Stone GW, Kappetein AP. Interpretation of results of pooled analysis of individual patient data. *Lancet*. 2018;392:818. Authors' reply.

30. Head SJ, **Milojevic M,** Domanski MJ, Farkouh ME, Kappetein AP. Stroke Risk Following Anaortic Off-Pump CABG Versus PCI. J Am Coll Cardiol. 2018;72:2861. Authors' reply.

31. Khan FM, Hameed I, **Milojevic M**, Wingo M, Krieger K, Girardi LN, Prager RL, Gaudino M. Quality metrics in coronary artery bypass grafting. Int J Surg. 2019; In press.

Book chapter

32. **Milojevic M,** Kohl PH, Frames S, Sousa-Uva M: "Differences and Similarities Between American and European Myocardial Revascularization Guidelines". In: Coronary artery Bypass Grafting. By: Taggart DP (Editor), and Puskas JD (Editor). Oxford University Press. In press.

Chapter 23

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Chapter 24

About the author



Milan Milojevic was born on December 1, 1985, in Belgrade, Serbia. He attended "Nadezda Petrovic" Medical School for nurse technicians in Zemun, from which he graduated in 2004.

Milan worked as a nurse anesthetist at the Department for Anesthesiology and Intensive Care in "Dedinje" Cardiovascular Institute (Belgrade, Serbia) between 2005-2013. While continuing to work full-time as a nurse practitioner, he started Medical School at the University of Belgrade in 2007. Alongside his medical studies, he completed several courses about the safe use of medical equipment in the operating theatre. Milan was invited to speak at several national and international nursing meetings. After completing 2nd year of medical school, he subsequently started his scientific research under the direct supervision of Prof. Miomir Jovic, which resulted in his first publication in a student peer-reviewed journal "*Medicinski Podmladak*". In 2013 he graduated from Medical School among the first in his class, a half year before schedule.

In the same period of time, Milan received the ERAWEB grant from the European Union's Erasmus Mundus Programme for further academic education. This grant enabled him to start Master of Science in Clinical Epidemiology studies at the Netherlands Institute for Health Science (NIHES) and Erasmus University Medical Center (MC) in Rotterdam, the Netherlands. The Master's program consisted of months of intensive coursework, summer and winter schools followed by six months of the scientific research. For his research project, Milan worked at the Departments of Epidemiology and Cardio-Thoracic Surgery under the supervision of Prof. Myriam Hunink and Prof. A. Pieter Kappetein.

After obtaining his Masters degree in Clinical Epidemiology (2014), he moved back to "Dedinje" Cardiovascular Institute and started as a resident in the Department of Anesthesiology and Intensive Care. Parallel to his medical training in Belgrade, Milan continued scientific research at the Department of Cardio-Thoracic Surgery, Erasmus University Medical Center, under the supervision of Prof. A.P. Kappetein and Dr. Stuart J. Head. In February 2016 he moved back to the Netherlands to continue his PhD program at Erasmus MC. His work focuses on decision-making regarding treatment of patients requiring myocardial

revascularization, the design of clinical trials and the development of clinical practice guidelines.

In October 2015 and November 2016, Milan's scientific work was awarded by the Cardiovascular Research Foundation (CRF) during the Transcatheter Cardiovascular Therapeutics (TCT) conferences in San Francisco and Washington DC, United States. Moreover, the research project of Milan and his colleagues, "Cause of death following PCI and CABG from the SYNTAX trial" was honored to be selected by the editorial board of the Journal of American College of Cardiology (JACC) as the highlighted article of 2016. In 2018, Milan was awarded the prestigious EACTS Francis Fontan Scholarship, which allows him to work as a fellow for the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC) Programme at the University of Michigan, Ann Arbor, United States. This group has a longstanding interest in cardiovascular outcomes research and in improving the care of adult cardiac and general thoracic surgery patients. Under the direct supervision of Prof. Richard L. Prager, he completed the dedicated fellowship training, acquiring knowledge and experience in the field of quality improvement and safety of cardiac surgical care.

Since February 2016, he has worked as a fellow for the Clinical Committee of the European Association of Cardio-Thoracic Surgery (EACTS), joining several task forces to obtain the most relevant and complete evidence to answers on specific medical questions. These expert groups have developed several clinical practice guidelines to assist in improving treatment decision making and health care policy in the field of cardio-thoracic surgery. Under the supervision of leading experts in the areas of cardiothoracic surgery, cardiology, and anesthesiology, he gained additional skills and wisdom for the development, dissemination, and implementation of practice guidelines into daily practice. In October 2017, Milan was elected by the European Association of Cardio-Thoracic Surgery (EACTS) to become a regular member of the EACTS Guidelines Committee. Moreover, he is a peer reviewer of the *Perfusion*, *European Journal of Cardio-Thoracic Surgery, British Medical Journal,* and *European Heart Journal,* and a member of the editorial board of the *Interactive CardioVascular and Thoracic Surgery.* After obtaining PhD degree, Milan will continue to strive to enhance the quality of life of those affected by cardiovascular disease through evidence-based medicine.

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The clinical goals for the care of each patient with complex coronary artery disease are to ensure that the most appropriate treatment is selected, and the best available evidence is used to guide procedural techniques and modify risk factors that could impact life expectancy and health-related quality of life. In this thesis, efficient surgical techniques, post-procedural therapies, and the most critical determinants for clinical decision-making between surgical and catheter-based myocardial revascularization are explored, thereby helping patients and treating physicians to choose the most appropriate revascularization strategy and secondary prevention therapy based on an individualized risk-benefit ratio. With the increasing number of high-quality clinical studies and rigorously developed clinical practice guidelines, a future-directed intention needs to be the implementation of quality-improvement programs across clinical microsystems to increase the use of evidence-based practice in hospitals and outpatient settings to enhance the efficacy and safety of patient care.



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