MANAGEMENT OF HOME MEDICATIONS IN PATIENTS UNDERGOING SURGERY

CHALLENGES IN OBTAINING EVIDENCE IN PERIOPERATIVE MEDICINE

LYNN A. MIGGELBRINK

Management of home medications in patients undergoing surgery

Challenges in obtaining evidence in perioperative medicine

Lynn Ann Miggelbrink

© copyright Lynn Ann Miggelbrink, 2026

Cover design: Inge van Loon
Printing: ProefschriftMaken || www.proefschriftmaken.nl
ISBN 978-94-6534-700-4
Pagina's 178

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the author or the copyright-owning journals for previously published chapters.

Management of home medications in patients undergoing surgery

Challenges in obtaining evidence in perioperative medicine

Beleid van thuismedicatie bij patiënten die een operatie ondergaan.
Uitdagingen bij het verkrijgen van bewijs in de perioperatieve geneeskunde

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. ir. W. Hazeleger,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

dinsdag 8 december 2026 des middags te 14.15 uur

door

Lynn Ann Miggelbrink

geboren op 30 december 1992
te Geleen

Promotor:

Prof. dr. W.A. van Klei

Copromotoren:

Dr. J.A.R. van Waes
Dr. T.H. Kappen

Beoordelingscommissie:

Prof. dr. M. den Heijer
Prof. dr. J. Hermanides
Prof. dr. R.G. Hoff
Prof. dr. M.C. Verhaar
Prof. dr. M.R. Vriens (voorzitter)

TABLE OF CONTENTS

Chapter 1 9

General Introduction

Part I - ANGIOTENSIN INHIBITORS IN THE PERIOPERATIVE PHASE 19

Chapter 2 21

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the peri-operative period: to withdraw or to continue? A multicentre randomised controlled trial. A study protocol.

Chapter 3 35

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the peri-operative period: to withdraw or to continue? A multicentre randomised controlled trial

Chapter 4 61

Adherence to medication intake instructions before surgery in patients taking renin-angiotensin system inhibitors

Part II – INTRAOPERATIVE CORTICOSTEROID ADMINISTRATION 71

Chapter 5 73

Peri-operative corticosteroid supplementation guideline adherence

Chapter 6 81

Effects of a supra-physiological corticosteroid regime in surgical patients at risk for tertiary adrenal insufficiency, a retrospective cohort study

Chapter 7 99

Efficacy of perioperative glucocorticoid supplementation in surgical patients at risk of tertiary adrenal gland insufficiency on quality of recovery, an observational cohort study

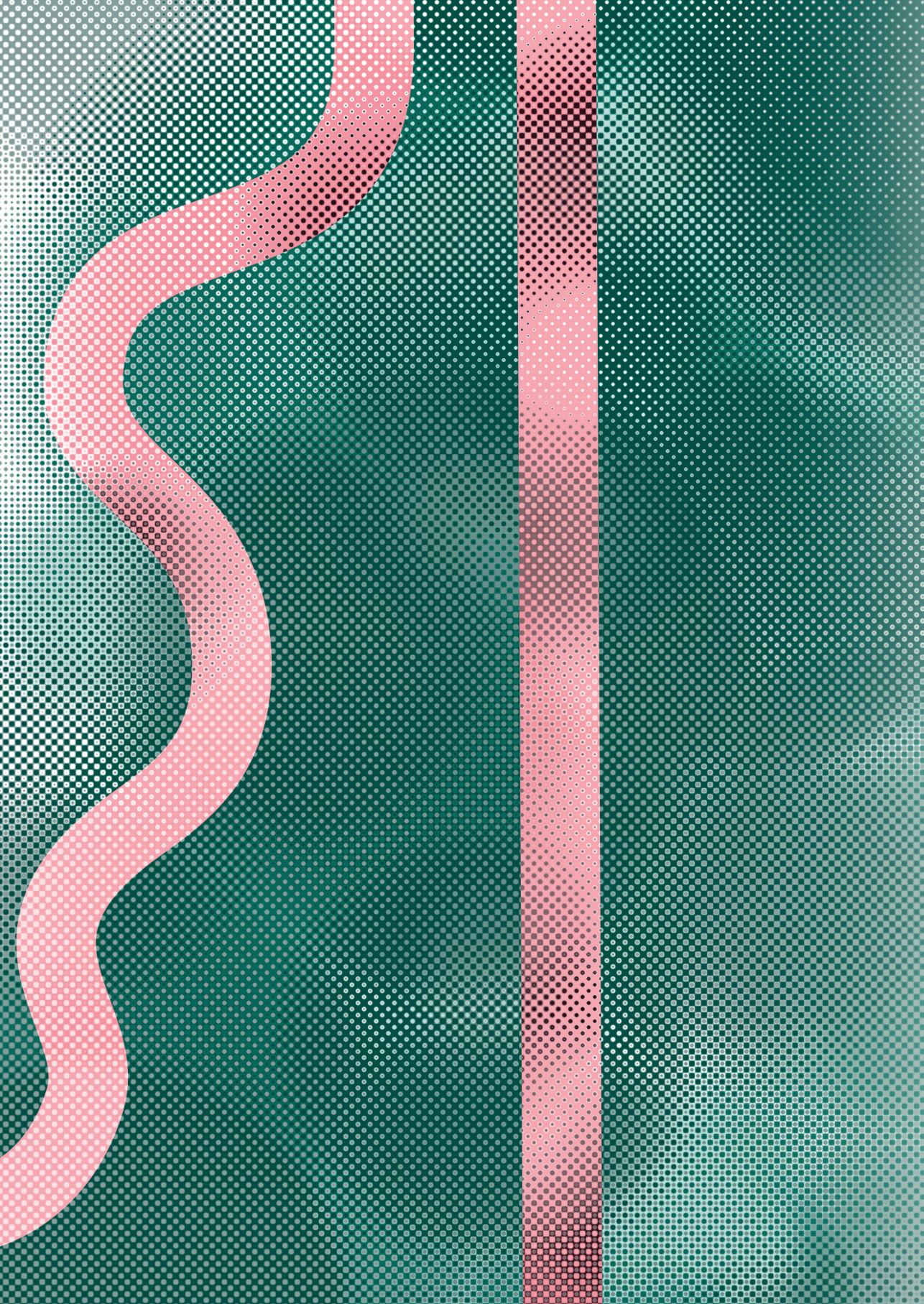
Chapter 8 119
Dutch guideline to prevent perioperative pulmonary complications
Dutch title: Protocol ter preventie van perioperatieve pulmonale complicaties

Part III – GENERAL DISCUSSION 145

Chapter 9 147
General Discussion

Part IV – ADDENDUM 163

Chapter 10 165
General summary 167
Dutch summary | Nederlandse samenvatting 170
Acknowledgements | Dankwoord 173
About the author 177
List of publications 178



CHAPTER 1

General Introduction

For most surgical procedures, some form of anesthesia is required, including locoregional techniques with or without general anesthesia. Although anesthesia is generally safe, the associated risks depend on both patient-related factors, such as underlying comorbidities, and surgery-specific risks. As patients requiring surgery are becoming increasingly older, present with multiple comorbidities, and frequently use several chronic medications, their overall perioperative risk profile is evolving.

To effectively manage these risks, in the past two decades anesthesiologists have become involved in the care for these patients from before to after surgery. Key areas of recent evidence-based developments in perioperative medicine include improvements in preoperative assessment of patients with cardiac diseases, the perioperative use of antihypertensives including beta-blockers, and strategies to detect postoperative myocardial injury.(1)

An area in perioperative medicine that lacks robust evidence is the management of chronic medications in patients with long-standing diseases. Many questions persist regarding perioperative continuation versus discontinuation, drug interactions, and the impact on meaningful clinical outcomes, underscoring an important gap in evidence-based guidance. Examples of this problem include the use of angiotensin inhibitors during the perioperative period, the administration of glucocorticosteroids in patients with (potential) tertiary adrenal insufficiency and the perioperative treatment of patients with chronic pulmonary disease with corticosteroids.

PERIOPERATIVE MANAGEMENT OF CHRONIC MEDICATION

(Dis)continuation of angiotensin inhibitors around surgery

Renin-Angiotensin System inhibitors (RASi), including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are commonly prescribed to treat hypertension. Other indications include heart failure, kidney disease, post-myocardial infarction, secondary prevention, and chronic migraines. Their blood pressure lowering effect results from inhibition of the renin-angiotensin-aldosterone system. Although a meta-analysis has indicated that temporary discontinuation of these drugs may reduce the risk of intraoperative hypotension, evidence regarding the impact of

continuation or discontinuation on postoperative complications, more specifically acute kidney injury (AKI), was lacking.(2) AKI is associated with adverse postoperative outcomes and it has long been assumed that AKI is exacerbated by anesthesia-induced hypotension, especially when RASi are continued in the perioperative period.(3–6) We therefore aimed to compare the effect of temporary discontinuation vs continuation of RASi on acute kidney injury (AKI) in a parallel, open-label, multicenter RCT including patients who used RASi to treat hypertension.(4,7,8)

Glucocorticoid supplementation around surgery

Corticosteroids carry a different kind of complexity. They can be lifesaving for patients who depend on them, harmful when overused, and controversial when evidence is thin. For some indications in the perioperative setting, corticosteroid supplementation is controversial. Corticosteroids are often used by patients with auto-immune diseases or following transplant surgery because of their anti-inflammatory and immune modulatory effects.(9–11) However, their use is not without drawbacks, particularly concerning their impact on adrenal gland function. The zona fasciculata of the adrenal gland produces steroid hormones such as cortisol, regulated by the hypothalamic-pituitary-adrenal (HPA) axis in a circadian rhythm.(12) Adrenal insufficiency (AI) refers to the reduced production of cortisol, and can be classified as primary, secondary or a tertiary adrenal insufficiency, depending on the site of dysfunction. Primary AI results from adrenal gland failure (e.g. Addison's disease), and secondary AI is due to pituitary or hypothalamic dysfunction. Tertiary AI is also known as steroid-induced AI and typically caused by prolonged glucocorticoid therapy suppressing the HPA-axis.(13) Patients on long-term corticosteroid therapy are at risk of developing adrenal atrophy and consequently tertiary AI. Daily oral glucocorticoid doses exceeding 5mg prednisone (or equivalent), are assumed to be sufficient to suppress the HPA-axis.(13,14) These patients may be vulnerable to developing an adrenal crisis during stress-inducing events, such as illness or surgery due to an inadequate endogenous cortisol response.

Symptoms of AI can range from atypical complaints, such as fatigue or weight loss, to severe, life-threatening hemodynamic shock during adrenal crisis.(13,15) To prevent a perioperative adrenal crisis and its associated refractory shock, administration of a perioperative stress-dose of corticosteroids is recommended. However, the evidence supporting this preventive strategy remains very limited.(16) Although

guidelines recommend the use of glucocorticoids, this is not consistently implemented in clinical practice, as many clinicians consider the risk of an adrenal crisis negligible.

Corticosteroid therapy around surgery

A specific reason for patients to be prescribed corticosteroids in the perioperative period is underlying chronic pulmonary disease. Similar to prescriptions to treat an exacerbation of chronic pulmonary disease, they are used to prevent postoperative pulmonary complications in patients with such chronic conditions.(9,17–19) In the Netherlands, in patients with chronic pulmonary disease, guidelines recommended perioperative administration of corticosteroids to prevent postoperative pulmonary complications, such as atelectasis, bronchospasms and infections.(20,21) Although this is not a widely adopted practice internationally and the supporting evidence is limited, it remained part of the national protocol up until October 2025.

Thesis objectives

The objectives of this thesis were to 1) investigate whether RASi should be discontinued around major non-cardiac surgery in patients using these drugs as treatment for hypertension, 2) to investigate guideline adherence of perioperative glucocorticoid administration in patients with suspected tertiary adrenal gland insufficiency, and its effect on postoperative symptoms and quality of recovery, and 3) to study guideline adherence for glucocorticoid therapy in patients with chronic pulmonary disease at risk for postoperative pulmonary complications.

Outline of the thesis

Part I (chapters 2, 3 and 4) describes a randomized clinical trial whose objective was to study the effect of continuing or withdrawing angiotensin inhibitors in the perioperative phase on postoperative AKI and other outcomes. Although the study was terminated early and this research question could not be answered, we described the lessons learned from this trial. Furthermore, in a subgroup, we investigated the adherence to instructions regarding intake of this medication.

Part II describes the evaluation of two indications of glucocorticoid supplementation in the perioperative phase. Chapters 5, 6 and 7 describe the investigation of patients with a possible tertiary adrenal gland insufficiency undergoing non-cardiac surgery. Chapter 5 describes adherence to the protocol regarding the perioperative administration of

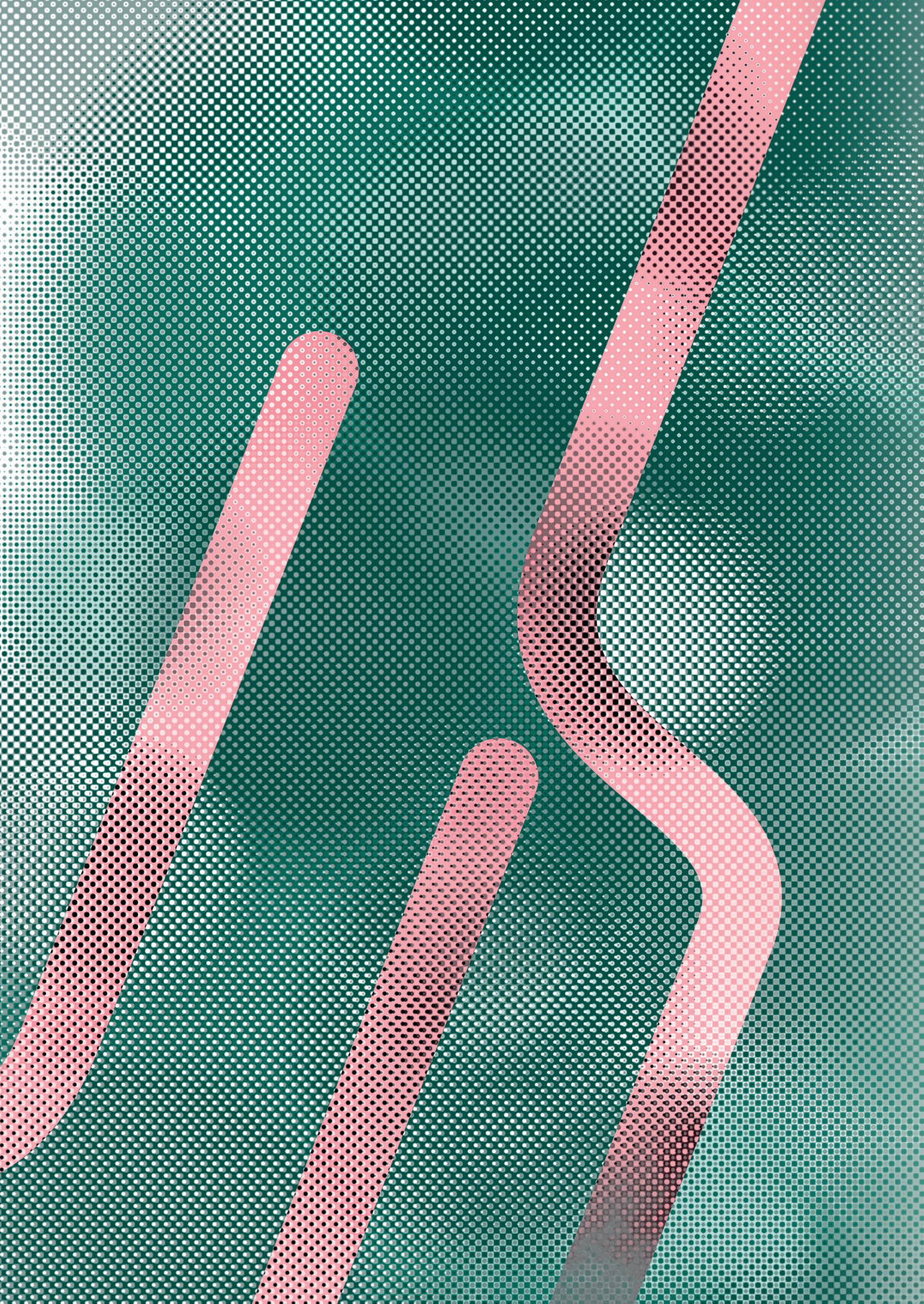
a stress dose of corticosteroids. Chapter 6 describes a retrospective study about possible symptoms associated with tertiary adrenal insufficiency in patients who did and did not receive a corticosteroid stress dose. Finally, chapter 7 reports a prospective study in which the quality of recovery in the same patient population was investigated. Chapter 8 describes reasons for non-adherence to glucocorticoid supplementation to prevent pulmonary complications around surgery in patients with obstructive pulmonary disease.

The final chapter (chapter 9) provides a general discussion of the topics explored in this thesis, reflecting on perioperative research, clinical practice, and protocol implementation. It considers the impact of evidence generation, human and organizational factors, and systemic challenges on improving patient care and translating knowledge into practice.

REFERENCES

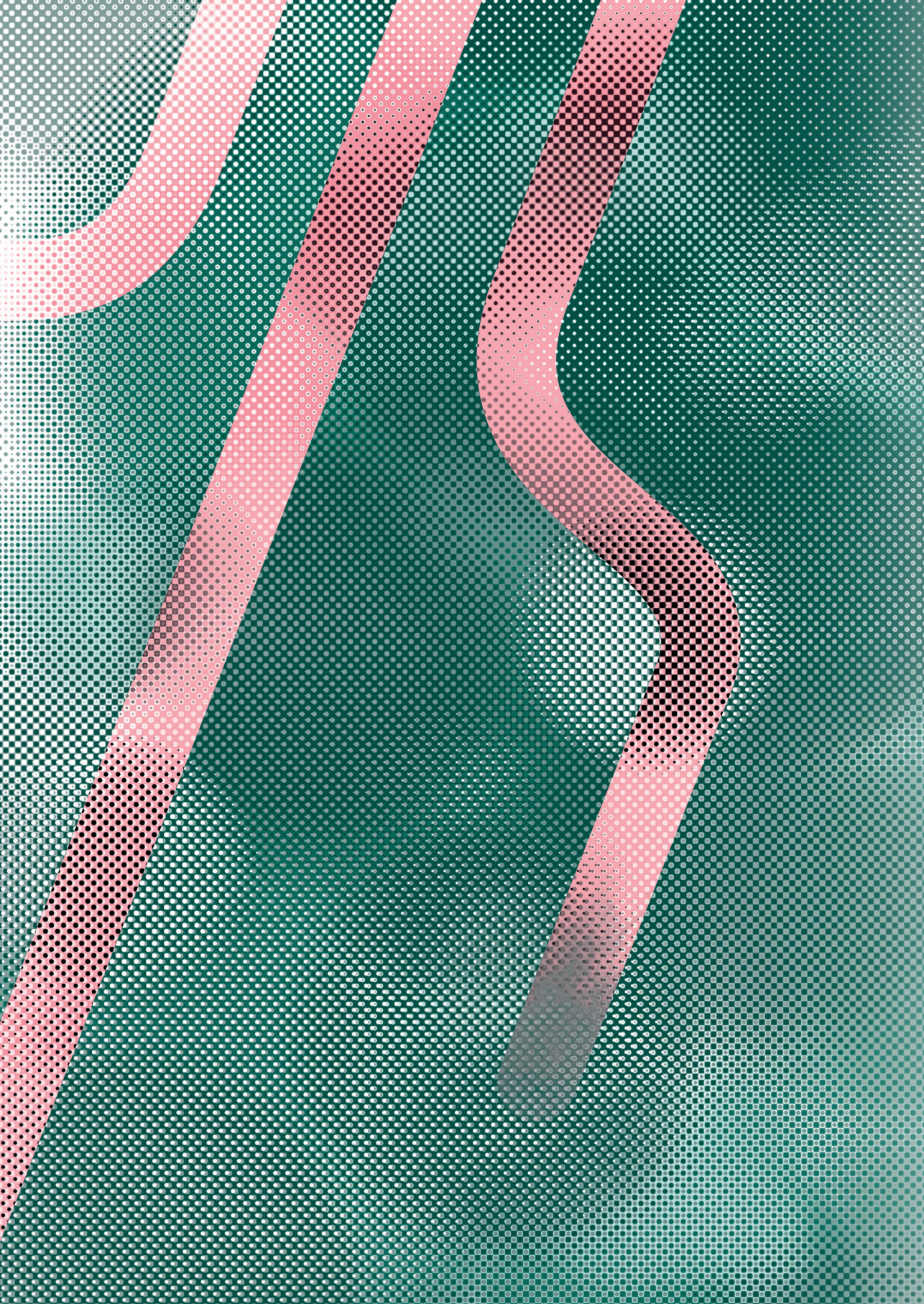
1. Fleisher L.A. Evidence-Based Practice of Anesthesiology. 4th ed. 2022.
2. Hollmann C, Fernandes NL, Biccard BM. A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before noncardiac surgery. Anesth Analg. 2018;127(3):678–87. doi:10.1213/ANE.0000000000002837
3. Van Waes JAR, Van Klei WA, Wijeysundera DN, Van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology. 2016;124(1):35–44. doi:10.1097/ALN.0000000000000922 PubMed PMID: 26540148.
4. Meersch M, Schmidt C, Zarbock A. Perioperative Acute Kidney Injury: An Under-Recognized Problem. Anesth Analg. 2017;125(4):1223–32. doi:10.1213/ANE.0000000000002369
5. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121(4):706–21. doi:10.1016/j.bja.2018.04.036
6. Van Waes JAR, Grobben RB, Nathoe HM, Kemperman H, De Borst GJ, Peelen LM, et al. One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury. Anesth Analg. 2016;123(1):29–37. doi:10.1213/ANE.0000000000001313 PubMed PMID: 27111647.
7. KDIGO Clinical Practice Guideline for Acute Kidney Injury [Internet]. Vol. 2. 2012;2(1). Available from: http://www.kidney-international.org
8. Van Waes JAR, Nathoe HM, De Graaff JC, Kemperman H, De Borst GJ, Peelen LM, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation. 2013;127(23):2264–71. doi:10.1161/CIRCULATIONAHA.113.002128 PubMed PMID: 23667270.
9. Fauci AS. Corticosteroids in autoimmune disease. Hosp Pract (Off Ed). 1983 Oct;18(10):99–103, 107–18, 113–4. doi:10.1080/21548331.1983.11702661 PubMed PMID: 6413383.
10. Tarantino A, Montagnino G, Ponticelli C. Corticosteroids in kidney transplant recipients. Safety issues and timing of discontinuation. Drug Saf. 1995 Sep;13(3):145–56. doi:10.2165/00002018-199513030-00002 PubMed PMID: 7495501.
11. Dashti-Khavidaki S, Saidi R, Lu H. Current status of glucocorticoid usage in solid organ transplantation. World J Transplant. 2021 Nov 18;11(11):443–65. doi:10.5500/wjt.v11.i11.443 PubMed PMID: 34868896.
12. Nicolaides NC, Charmandari E, Kino T, Chrousos GP. Stress-Related and Circadian Secretion and Target Tissue Actions of Glucocorticoids: Impact on Health. Front Endocrinol (Lausanne). 2017;8:70. doi:10.3389/fendo.2017.00070 PubMed PMID: 28503165.
13. Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clin Chim Acta. 2020 Jun;505:78–91. doi:10.1016/j.cca.2020.01.029 PubMed PMID: 32035851.
14. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM. 2000 Feb;93(2):105–11. doi:10.1093/qjmed/93.2.105 PubMed PMID: 10700481.

15. Kaufman G. Capacity to handle unassimilable material: coping strategies of schizophrenics and normals. J Pers Assess. 1973 Dec;37(6):519–26. doi:10.1080/00223891.1973.10119916 PubMed PMID: 4588051.
16. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – A systematic review. Dan Med J. 2018;65(6):1–5. PubMed PMID: 29886882.
17. Walters JAE, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014 Sep 1;2014(9):CD001288. doi:10.1002/14651858.CD001288.pub4 PubMed PMID: 25178099.
18. Bleecker ER, Al-Ahmad M, Bjermer L, Caminati M, Canonica GW, Kaplan A, et al. Systemic corticosteroids in asthma: A call to action from World Allergy Organization and Respiratory Effectiveness Group. World Allergy Organ J. 2022 Dec;15(12):100726. doi:10.1016/j.waojou.2022.100726 PubMed PMID: 36582404.
19. Snell GI, Westall GP, Paraskeva MA. Immunosuppression and allograft rejection following lung transplantation: evidence to date. Drugs. 2013 Nov;73(16):1793–813. doi:10.1007/s40265-013-0136-x PubMed PMID: 24142409.
20. Yang CK, Teng A, Lee DY, Rose K. Pulmonary complications after major abdominal surgery: National Surgical Quality Improvement Program analysis. Journal of Surgical Research. 2015;198:441–9. doi:10.1016/j.jss.2015.03.028
21. Anesthesiologie NV voor. Nederlandse Vereniging voor Anesthesiologie [Internet]. 2012. p. 1–121. Richtlijn Preventie van perioperatieve pulmonale complicaties bij niet-pulmonale chirurgie bij patienten met een verhoogd risico op pulmonale complicaties. Available from: https://www.anesthesiologie.nl/uploads/files/KD_RL_Preventie_pulmonaal_belaste_patient_2012.pdf



PART I

ANGIOTENSIN INHIBITORS IN THE PERIOPERATIVE PHASE



CHAPTER 2

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the peri-operative period: to withdraw or to continue? A multicentre randomised controlled trial. A study protocol.

L.A. Miggelbrink (1), W.A. van Klei (1,5), J.A.R. van Waes (1)
Departments of 1. Anesthesiology, from the University Medical Centre Utrecht, Utrecht University, the Netherlands.

Not published, manuscript

ABSTRACT

Background: Angiotensin inhibitors are frequently used to treat hypertension. Patients who continue using angiotensin inhibitors when undergoing surgery, are at risk of hypotension in the perioperative period, which can lead to organ hypoperfusion and damage. It differs between countries, hospitals and anesthesiologists if it is recommended to continue or to temporarily withdraw these drugs. The latest research on this topic suggests that perioperative continuation may lead to more complications, but definitive evidence is lacking. The aim of this trial is to assess whether angiotensin inhibitors should be withdrawn or continued in the perioperative period.

Methods and analysis: The AIPOP trial is a multicenter, pragmatic randomized controlled trial. Patients ages 18 years and older, undergoing intermediate to high-risk elective non-cardiac surgery, who chronically use angiotensin inhibitors to treat hypertension, are eligible for inclusion in the absence of exclusion criteria. The study is set to include 3200 patients, 1600 per arm. Patients will be randomized 1:1 to either continuing or temporarily withdrawing their angiotensin inhibitor. If the patient was randomized to temporarily stopping their angiotensin inhibitor, the drug would be stopped 24 hours before surgery and would be resumed on the second or third postoperative day, as soon as the clinical condition allowed it based on judgement by the attending physician. The primary outcome is the development of an acute kidney injury based on the KDIGO guideline. Blood will be drawn before surgery to determine baseline values of creatinine and troponin, as well as on the first and second postoperative day (where possible). Postoperative complications are inventoried until discharge. Follow-up will occur 4 weeks and 3 months after surgery, to inventory secondary outcomes, including medical events, as well as quality of life and disability free survival.

Discussion: This trial will investigate whether angiotensin inhibitors should be continued or temporarily withdrawn in the perioperative period, as current evidence is lacking. If no difference in outcomes is found, temporarily withdrawing angiotensxin inhibitors would be unnecessary.

Trial registration and ethics: ClinicalTrials.gov identifier NCT04506372. Registered on August 10, 2020. Ethical approval was granted by the Research Ethics Committee (NedMec 20/027).

Funding: Zon MW Goed Gebruik Geneesmiddelen Project number 848018007. No other external funding.

Key words: Non-cardiac surgery, angiotensin inhibitors, perioperative management, acute kidney injury, quality of life, disability free survival

INTRODUCTION

Many patients undergoing surgical procedures, suffer from cardiovascular diseases. Approximately one-third of surgical patients use angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for the treatment of hypertension.(1,2) These drugs cause vasodilatation through inhibition of the renin-angiotensin-aldosterone system (RAAS), lowering the blood pressure. Through their effect on blood pressure, these drugs may induce perioperative hypotension. Especially as one of the most common effects of anesthesia and surgery on the cardiovascular system is hypotension, especially in patients with cardiovascular disease. Concurrent use of ACEi or ARB on top of the anesthetic side effects, blocks the physiological response from RAAS to hypotension. Thus, hypotension may contribute to decreased tissue perfusion, which can lead to organ failure and death.(1,3,4) However, withdrawal of renin-angiotensin-aldosterone system inhibitors (RASi), may increase RAAS activity, blood pressure and systemic vascular resistance. This too may impair regional circulation.(5) Both the heart and kidneys are vulnerable to injury caused by poor tissue perfusion, such as perioperative hypotension.(6–8) Both perioperative acute kidney injury and myocardial injury occur frequently, and are associated with poor prognosis.(2,7,9)

The available evidence on this topic suggests that perioperative continuation of RASi is associated with an increased incidence of intra- and postoperative hypotension, but that withdrawal may increase the incidence of intra- and postoperative hypertension. A meta-analysis showed that hypotension occurs in 28% of patients who continued RASi, and that patients who were not administered RASi on the morning of surgery, had significantly lower risk of intraoperative hypotension (23% versus 30%; OR 0.63; 95% CI, 0.47–0.85).(4) Furthermore, intraoperative hypotension is associated with hypotension and acute kidney injury (AKI), postoperative myocardial injury (POMI) and death. The risk of AKI increased two- to five-fold, the risk of POMI increased two-to four-fold, and the risk of death increased two-fold after postoperative hypotension.(8,10) Hence, perioperative withdrawal of RASi may prevent postoperative complications and improve patient outcomes through the prevention of perioperative hypotension. However, these findings from cohort studies might be based bias due to residual confounding, and too small, randomized studies. Therefore, it is still unknown if RASi should be continued or withdrawn in the perioperative period. Current

guidelines on this topic are contradictory: the American guidelines advise continuation of RASi, whereas the European and Canadian guidelines advise withdrawal of RASi in the perioperative period. (11,12) Consequently, policies vary between hospitals and anesthesiologists.(13)

Currently, there is an important knowledge gap about the continuation or withdrawal of RASi in the perioperative period.(1,14,15) The results of this study are expected to be incorporated in future updates of both national and international guidelines about perioperative management. (11,16)

METHODS

This is a pragmatic, multicenter, randomized clinical trial performed in multiple hospitals both in the Netherlands and abroad. Eligible patients are patients who use RASi chronically as treatment for hypertension undergoing (semi-)elective, intermediate to high-risk non-cardiac surgery according to the ESC, with an admission of at least two postoperative nights. Exclusion criteria include severe chronic kidney disease (defined as an estimated glomerular filtration rate <30 ml/min/1.73 m2), a history of chronic systolic heart failure (defined as left ventricular ejection fraction ≤40%), a ST-elevation myocardial infarction within one year (defined according to the fourth universal definition of myocardial infarction), transplant surgery, a combination pill with a drug other than a diuretic (including calcium channel blockers, beta-blockers and neprilysin inhibitors), use of drugs acting on the RAAS other than RASi (e.g. aliskiren), repeat trial participants, urgent or emergent surgery (defined as surgery within 48 hours of diagnosis), surgical procedures associated with decreased kidney function or perioperative blood pressure changes (e.g. nephrectomy or pheochromocytoma), carotid surgery, and an inability to manage medications.(17)

Recruitment

Eligible patients receive study information during or after their visit to the preoperative assessment clinic, after which they will receive sufficient time to consider participation. Written informed consent will be obtained by study personnel up to one day before surgery at the latest.

Randomization

Approximately one week before surgery patients will be randomized to either continue or withdraw the RASi. Computer generated, variable block (4, 6, 8) randomization will be used to allocate patients (1:1) with stratification based on institute, and whether the RASi is a combination pill. The patient and all caregivers are informed of the allocation. As this is a pragmatic trial, no concealment of randomization is present. The outcomes will be assessed blinded for the intervention.

Intervention

Patients are randomized to either continuing RASi (control) or temporarily discontinuing RASi (intervention). If patients are randomized to the intervention, RASi is discontinued 24 hours before surgery. Depending on the patient's postoperative clinic, it can be restarted on the second or third postoperative day. As the randomization is not blinded, all caregivers are notified on the randomization.

Study procedures

After signing informed consent, but before the study procedure, patients will be asked to fill out two questionnaires, the EuroQoL 5-Dimension (EQ-5D) questionnaire about quality of life and the World Health Organization Disability Assessment Schedule (WHODAS) about disability. These questionnaires are repeated at four weeks and three months after surgery.

Blood will be drawn before surgery to determine baseline troponin and creatinine levels. The creatinine levels will be determined for the first two postoperative days, whereas the troponin level will be determined on the first postoperative day. After being discharged from the hospital, patients are asked to have blood drawn in the first three postoperative months, to have the creatinine determined.

At least one day before surgery, the patient will be randomized to either continue or temporarily withdraw their RASi. This will be communicated with the patient. If the patient is randomized to temporarily stop using their RASi, this is in the 24 hours preoperatively to 48 or 72 hours postoperatively. Timing of all study activities are depicted in Table 1.

To determine if patients adhered to the strategy they were allocated to, patients will be requested to keep a medication diary for RASi in the week prior to the surgery. To determine postoperative adherence after

discharge, patients will be asked to send empty medication packaging to be used as a proxy to determine adherence.

Primary outcome

The primary outcome is AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (e.g. an absolute creatinine increase of ≥26.5 µmol/l or an increase of ≥1.5 times baseline).

Secondary outcome

Further outcomes of interest include the development of postoperative complications during admission such as POMI in the first two postoperative days (defined as an increased level of serum troponin above the clinical cut-off value), and postoperative delirium (based on the Delirium Observation Screening). Intraoperative (from the start of anesthesia until the end of surgery) and postoperative (from the end of surgery up to and including the second postoperative day) hypotension (defined as a mean arterial pressure <65 mmHg) were investigated. The intraoperative use of drugs to maintain blood pressure were inventoried as well.

Complications within three months investigated included major cardiovascular complications (e.g. myocardial infarction, coronary revascularization, heart failure, arrhythmia, stroke), all-cause mortality, kidney function, and end-stage renal disease (defined as requiring dialysis or transplantation).

The length of stay in the hospital or nursing home are determined. The quality of life (as determined by EQ-5D) and disability (as determined by WHODAS) are investigated at four weeks and three months.

Safety outcomes included the development of perioperative heart failure (as clinically diagnosed by the attending physician or cardiologist), and hypertension in the perioperative period. Perioperative hypertension was defined as preoperative hypertension within 24 hours before start of anesthesia or postoperative hypertension within two days after surgery (defined as a systolic blood pressure >180mmHg or a diastolic blood pressure >110mmHg).

Sample size calculation

The incidence of AKI was estimated to be 10% based on literature and previous data. However, other studies referred to in the KDIGO guideline

reported an AKI incidence of 10-22%.(7,18,19) To detect a risk reduction from 10% to 7% with a type 1 error rate of 0.05, power of 80%, and 10% loss to follow-up, in total approximately 3,200 patients are needed (n=1,600 per arm).

Data safety monitoring board

A data safety monitoring board was appointed to safeguard the interests of the trial participants, to assess the safety and efficacy of the intervention during the trial. It was stated that they would meet at least once a year, or for every 800 included patients.

The patient perspective

Four patient representatives were engaged in the set-up phase of the trial to ensure the study's relevance and study procedures to their needs, and to ascertain that the patient information provided was clear and comprehensible.

Statistical analysis

Baseline characteristics will be reported as counts (percentages), means (standard deviation), and medians (inter quartile range) where appropriate, and investigated using the chi-square test, t-test, and Mann-Whitney U test where appropriate.

The primary outcome AKI will be compared between the groups by using logistic regression analysis and will be expressed as an odds ratio (OR) with accompanying 95% confidence interval. Groups will be based on 'intention to treat' analysis. Sensitivity analysis of the primary outcome will be performed by using 'per protocol' analysis. The subgroups will be analyzed using logistic regression analysis and will be expressed as an odds ratio (OR) with accompanying 95% confidence interval. Subgroups are high risk surgery, pre-existing renal disease, age ≥70 years, gender, number of antihypertensive drugs, perioperative use of non-steroidal anti-inflammatory drugs, combination pill with diuretics, duration of withdrawal of RASi, RASi specific based on drug half-life and starting time of surgery.

Secondary outcomes will be analyzed using linear regression, logistic regression and Poisson regression where appropriate. In case of missing data, multiple imputation will be performed.

Table 1. Participant timeline

Time point		**Study period**						
	Enrolment	**Pre-allocation**	**Allocation**	**Post-allocation**				
	Screening and informed consent (T_1)	Preoperative (T_0)		Day of surgery (T_1)	Postop day 1 (T_2)	Postop day 2 (T_3)	4 weeks after surgery (T_4)	3 months after surgery (T_5)
Enrolment								
Eligibility screening	X							
Informed consent	X							
Randomization			X					
Questionnaires								
EQ-5D		X					X	X
WHODAS		X					X	X
Postoperative complications								X
Productivity costs								X
Bloodwork								
Creatinine				X	X	X *		X
Troponin				X	X			

* if still admitted to hospital

Abbreviations: EQ-5D, European Quality of Life Five Dimension; WHODAS, World Health Organization Disability Assessment Schedule

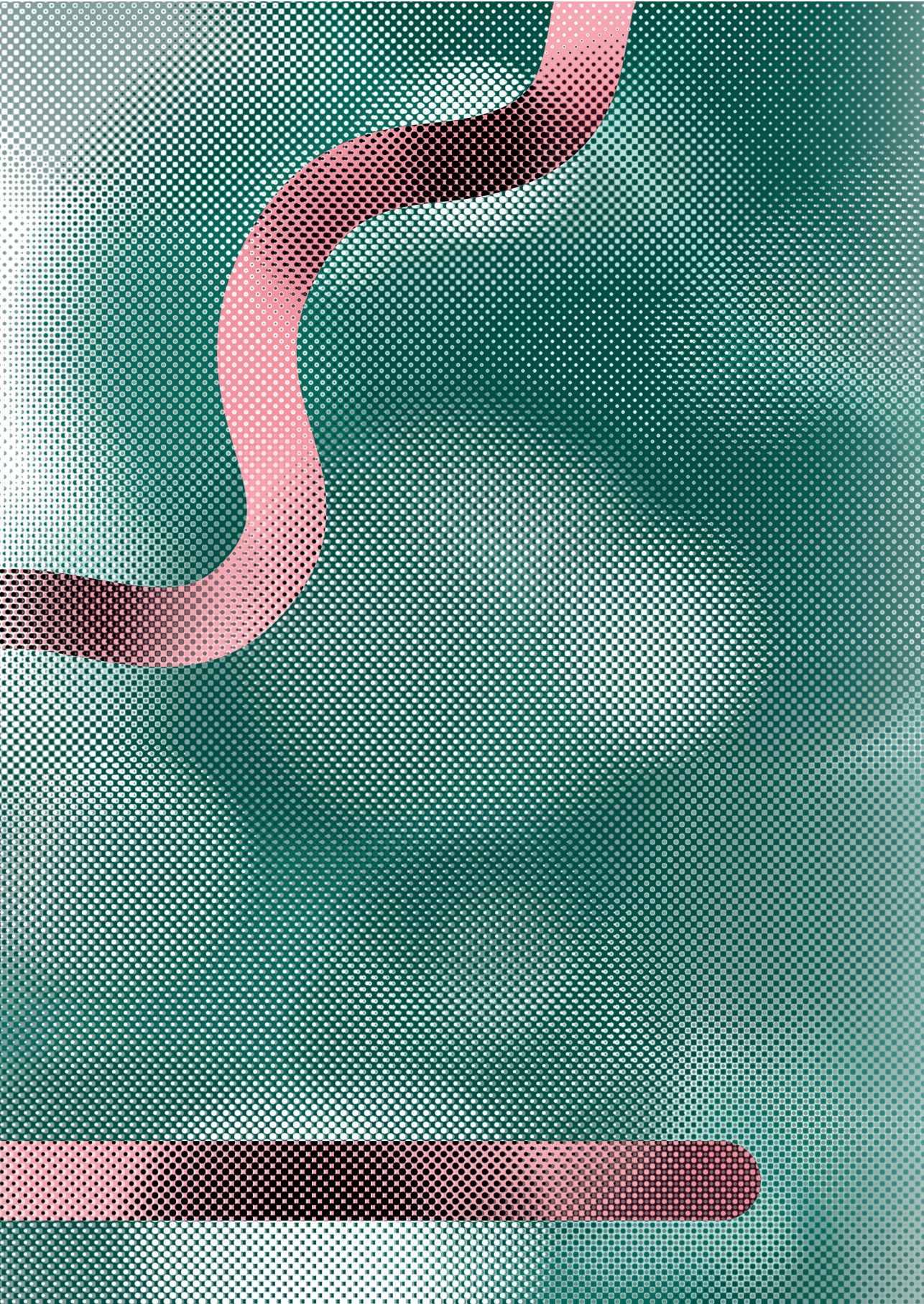
DISCUSSION

This study seeks to investigate a gap in knowledge in the perioperative care, namely if angiotensin inhibitors should be continued or temporarily withdrawn. Multiple small cohorts had been studied, before AIPOP and several other randomized trials were conducted (SPACE trial, PREOP-ACEi trial, STOPORNOT trial). All include different primary outcomes (e.g. POMI, intraoperative hypotension, composite endpoint all major complications), compared to AKI in our study.

REFERENCES

1. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z DP. Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery. Anesthesiology. 2017;(1):16–27.
2. Van Waes JAR, Grobben RB, Nathoe HM, Kemperman H, De Borst GJ, Peelen LM, et al. One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury. Anesth Analg. 2016;123(1):29–37.
3. Kheterpal S, Khodaparast O, Shanks A, O'Reilly M, Tremper KK. Chronic Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Therapy Combined With Diuretic Therapy is Associated With Increased Episodes of Hypotension in Noncardiac Surgery. J Cardiothorac Vasc Anesth. 2008;22(2):180–6.
4. Hollmann C, Fernandes NL, Biccard BM. A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before noncardiac surgery. Anesth Analg. 2018;127(3):678–87.
5. Auron M, Harte B, Kumar A, Michota F. Renineangiotensin system antagonists in the perioperative setting: Clinical consequences and recommendations for practice. Postgrad Med J. 2011;87(1029):472–81.
6. Van Waes JAR, Van Klei WA, Wijeysundera DN, Van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology. 2016;124(1):35–44.
7. Meersch M, Schmidt C, Zarbock A. Perioperative Acute Kidney Injury: An Under-Recognized Problem. Anesth Analg. 2017;125(4):1223–32.
8. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth [Internet]. 2018;121(4):706–21. Available from: https://doi.org/10.1016/j.bja.2018.04.036
9. Van Waes JAR, Nathoe HM, De Graaff JC, Kemperman H, De Borst GJ, Peelen LM, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation. 2013;127(23):2264–71.
10. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth. 2019;122(5):563–74.
11. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur Heart J. 2014;35(35):2383–431.
12. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. Can J Cardiol. 2017 Jan;33(1):17–32.

13. Walker SLM, Abbott TEF, Brown K, Pearse RM, Ackland GL. Perioperative management of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers: a survey of perioperative medicine practitioners. PeerJ. 2018;6:e5061.
14. Nederlandse Vereniging voor Anesthesiologie. Richtlijn Preventie van perioperatieve cardiale complicaties bij niet-cardiale chirurgie. 2009;
15. Vassallo MC, Tartamella F, Testa F. Should we withhold angiotensin converting enzyme inhibitors before anaesthesia? An updated debate on the pros and cons. J Clin Anesth [Internet]. 2017;42:51–2. Available from: https://doi.org/10.1016/j.jclinane.2017.07.008
16. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Dev. Vol. 22, Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2015. 162–215 p.
17. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–69.
18. Zarbock A, Koyner JL, Hoste EAJ, Kellum JA. Update on perioperative acute kidney injury. Anesth Analg. 2018;127(5):1236–45.
19. Gameiro J, Fonseca JA, Neves M, Jorge S, Lopes JA. Acute kidney injury in major abdominal surgery: incidence, risk factors, pathogenesis and outcomes. Ann Intensive Care [Internet]. 2018;8(1):1–10. Available from: https://doi.org/10.1186/s13613-018-0369-7



CHAPTER 3

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the peri-operative period: to withdraw or to continue? A multicentre randomised controlled trial.

Subtitle: AIPOP

Lynn A. Miggelbrink (1), Wilton A. van Klei (1,4,5,6), Marianne C. Verhaar (2), Folkert W. Asselbergs (7,8,9), Wilko Spiering (3), Wolfgang F.F.A. Buhre (1) , Marcus W. Hollmann (10), Felix van Lier (11), Eric (H.) P.A. van Dongen (12), Patrick Schober (10), Thijs C.D. Rettig (13), Hans (J.) B. Reitsma (14), Eva P.C. van Schaik (1), Lisette M. Vernooij (1), Judith A.R. van Waes (1)

Departments of 1. Anaesthesiology, 2. Nephrology, 3. Vascular Medicine, University Medical Center Utrecht, Utrecht University, the Netherlands.
4. Department of Anaesthesiology and Pain Management, Toronto General Hospital, University Health Network Toronto, Ontario, Canada.
5. Department of Anaesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.
6. Department of Anaesthesiology and Pain Management, Toronto General Hospital Research Institute, Toronto, Ontario, Canada.
7. Department of Cardiology, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
8. Institute of Health Informatics, University College London, London, UK
9. The National Institute for Health Research University College London Hospitals Biomedical Research Centre, University College London, London, UK
10. Department of Anaesthesiology, Amsterdam University Medical Centres, Amsterdam, the Netherlands.
11. Department of Anaesthesiology, Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands.
12. Department of Anaesthesiology, St. Antonius Hospital, Nieuwegein, The Netherlands.
13. Department of Anaesthesiology and Intensive Care, Amphia Hospital, Breda, The Netherlands.
14. The Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, the Netherlands.

Published as a Science Letter
Br J Anaesth. 2025 Oct;135(4):1075-1077. doi: 10.1016/j.bja.2025.05.056. Epub 2025 Jul 22.

EDITOR,

Many surgical patients use renin-angiotensin system inhibitors (RASi), including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Although there is limited evidence, current guidelines recommend discontinuation before surgery in patients at risk of hypotension.(1–3) This lack of evidence remains a crucial knowledge gap in perioperative medicine and leads to varying practices among hospitals and individual physicians.(4,5) We therefore aimed to compare the effect of temporary discontinuation versus continuation of RASi on acute kidney injury (AKI). This trial was ended prematurely because of slow recruitment and therefore did not generate substantial evidence. Nevertheless, it provided crucial lessons that we wish to share as they may be relevant to any future trials in perioperative medicine.

We conducted a parallel, open-label, multicentre, randomised controlled trial (NCT04506372). All participants provided written informed consent and the local ethics committees approved the study protocol prior to patient recruitment (Medical Research Ethics Committee Utrecht; 20-027/D and University Health Network Toronto Research Ethics Board; 21-5815). Adult patients using RASi who were scheduled for elective major surgery with an anticipated postoperative length of hospital stay of at least two nights were eligible for inclusion. Patients were randomised to temporarily discontinue RASi therapy one day before surgery, and to resume on the second day after surgery. Participants assigned to perioperative continuation of RASi were instructed to continue this drug throughout the perioperative period. Perioperative care beyond randomisation was at the discretion of the treating physicians. The primary outcome was postoperative AKI. Based on previous studies in comparable populations and local retrospective data, we estimated the incidence of the primary outcome at 10%. To detect a reduction in AKI from 10% to 7% in the intervention group (discontinuing RASi), with a type 1 error rate of 0.05, a power of 80%, and accounting for 10% loss to follow-up, 3,200 patients were required (N=1,600 per arm) (Supplemental file S1).

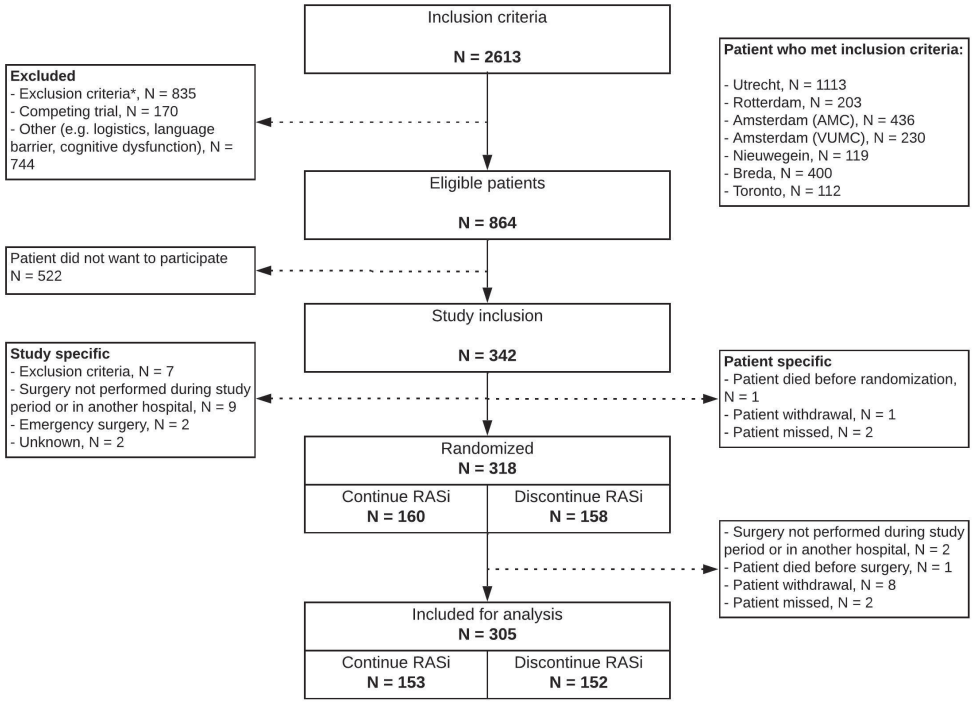
Between September 2020 and January 2023, we randomised 318 of the 2,613 patients who met the inclusion criteria and ultimately included 305 in the analysis (Figure 1). Their median age was 68 (IQR 61–75) years, with 63% of patients being male. The incidence of AKI was 4%, and no difference was observed between the two groups. However, because this

study was terminated early, it was underpowered to detect the anticipated difference in the primary outcome. No differences were observed for any of the other outcomes (Supplemental file S2).

The trial was terminated because of a continuing low inclusion rate after multiple attempts to increase inclusions, and in consultation with the data safety monitoring board and the grant provider. There were several reasons for the low inclusion rate. During and following the COVID-19 pandemic and subsequent personnel shortages, a substantial reduction in the number of surgical procedures was observed, and patients were discharged sooner to overcome shortage of available (staffed) hospital beds. In addition, surgeries were relocated to other hospitals. Further, in the design phase of the trial, a larger number of hospitals intended to participate. However, by the eventual start of the trial many hospitals were not able to participate due to not resolving logistical constraints related to the pandemic. In response to the low inclusion rate, we broadened the inclusion criteria and tried to recruit more participating centres. Despite these changes, centres that initially seemed interested considered the study not feasible because the study procedures (randomising individuals to an intervention outside the operating room area) or required resources, i.e. an established research infrastructure.

Importantly, several lessons were learned from this trial. First, we studied a simple intervention (continue or discontinue RASi therapy around surgery) and our trial followed a pragmatic design. As a substantial number of the target group was on RASi therapy, we expected that inclusion of patients would be relatively easy.(4,6) However, of the 2,613 patients who were eligible in the six participating hospitals in two and a half years, only 318 (12%) were randomised (Figure 1), i.e. an average of 20 patients per hospital per year. For comparison, the STOP-or-NOT trial, in which patients were randomly assigned to either continue or discontinue RASi therapy before surgery, recruited 2,222 patients in 40 hospitals over five years, i.e. an average of 11 inclusions per hospital per year.(7) Similarly, the SPACE trial comparing the impact of (dis)continuing RASi therapy included 262 patients in six hospitals in four years, again an average of 11 per year per hospital.(8) Although recruitment in these trials was interrupted by the COVID pandemic, These low inclusion rates are concerning examples for the previously described and persisting drop in recruitment rates in clinical trials.(9) Determination of relevant differences in outcomes that occur at incidences below 10% require large-sized trials. If even a simple intervention results

Figure 1. Flowchart



* Exclusion criteria were severe chronic kidney disease, chronic systolic heart failure, recent ST-elevated myocardial infarction, unable to self-manage chronic medication, and undergoing (partial) nephrectomy, pheochromocytoma surgery or transplant surgery.

Abbreviations: N, number; RASi, Renin-Angiotensin System inhibitors

in only 10-20 inclusions per hospital per year, trials will become difficult to manage and extremely expensive. Although suggestions to overcome the challenges in conducting large-sized trials in perioperative medicine were pointed out previously, successful completion of such trials is still challenging. In hindsight, a different design, e.g. cluster randomisation of hospitals instead of individual patients or applying practice-preference randomised consent, may have enhanced study feasibility.(10) Second, the observed incidence of AKI in this study was 4%, notably lower than the anticipated 10%. This may be explained by selection bias due to the exclusion of patients at high risk of AKI (those with severe chronic kidney disease or heart failure), or due to the healthy participant effect.(11,12) It is unlikely that the calculated power would have been achieved even if the study had reached the intended sample size. With the incidence of AKI we observed, the required sample size to be able to detect a 40% decrease in the incidence of AKI (from 5% to 3%) would have been approximately

8,440 patients. Whether or not such an investment is reasonable given the clinical relevance of a 2% absolute decrease is debatable.

In conclusion, this prematurely ended trial did not generate substantial evidence regarding the question whether RASi should be continued or discontinued around major surgery. The early termination of this trial highlights the importance of rethinking trial design in perioperative medicine. Alternative designs, such as cluster randomisation or practice-preference randomised consent, may enhance feasibility.

REFERENCES

1. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. Canadian Journal of Cardiology [Internet]. 2017;33(1):17–32. Available from: http://dx.doi.org/10.1016/j.cjca.2016.09.008
2. Thompson A, Fleischmann KE, Smilowitz NR, de las Fuentes L, Mukherjee D, Aggarwal NR, et al. 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Nov 5;150(19).
3. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022 Oct 14;43(39):3826–924.
4. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z DP. Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery. Anesthesiology. 2017;(1):16–27.
5. Vassallo MC, Tartamella F, Testa F. Should we withhold angiotensin converting enzyme inhibitors before anaesthesia? An updated debate on the pros and cons. J Clin Anesth [Internet]. 2017;42:51–2. Available from: https://doi.org/10.1016/j.jclinane.2017.07.008
6. Van Waes JAR, Grobben RB, Nathoe HM, Kemperman H, De Borst GJ, Peelen LM, et al. One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury. Anesth Analg. 2016;123(1):29–37.
7. Legrand M, Futier E, Leone M, Deniau B, Mebazaa A, Plaud B, et al. Impact of renin-angiotensin system inhibitors continuation versus discontinuation on outcome after major surgery: protocol of a multicenter randomized, controlled trial (STOP-or-NOT trial). Trials. 2019 Mar 5;20(1):160.
8. Ackland GL, Patel A, Abbott TEF, Begum S, Dias P, Crane DR, et al. Discontinuation vs. continuation of renin–angiotensin system inhibition before non-cardiac surgery: the SPACE trial. Eur Heart J. 2024 Apr 1;45(13):1146–55.
9. Wijeysundera DN, Mistry N, Mazer CD. The Future of Clinical Trials Methodology: Accomplishments and Challenges Ahead. Anesth Analg. 2022 Apr 7;134(4):664–7.
10. Myles PS, Dieleman JM, Munting KE, Forbes A, Martin CA, Smith JA, et al. Dexamethasone for Cardiac Surgery: A Practice Preference-Randomized Consent Comparative Effectiveness Trial. Anesthesiology. 2024 Nov 1;141(5):859–69.
11. Prowle J, Forni L, Bell M, Chew M, Edwards M, Grams M, et al. Postoperative acute kidney injury in adult non-cardiac surgery joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. Nat Rev Nephrol. 2021;17(9):605–18.
12. The healthy participant effect . . . and other stories. BMJ. 2024;386:q1580.

SUPPLEMENTARY FILES

S1. Supplementary Methods and Results

METHODS

Study design and setting

This study was a parallel, open-label, multicentre, randomised controlled trial registered at ClinicalTrials.gov (NCT04506372). The trial was conducted at six hospitals in the Netherlands (University Medical Centre Utrecht, Amsterdam University Medical Centre with two locations, Erasmus Medical Centre Rotterdam, Sint Antonius Hospital Nieuwegein, Amphia Hospital Breda) and one Canadian hospital (University Health Network Toronto). Individual patient randomisation to either continue or temporarily discontinue RASi therapy was performed using the electronic data capture system Castor EDC (Amsterdam, The Netherlands) with variable block randomisation (block sizes 4, 6, and 8) and stratification for the hospital where the patient underwent surgery. Both patients and healthcare providers were not blinded to the allocation status. Perioperative care beyond randomisation followed the standard of care and was determined by the treating physicians.

All participants provided written informed consent and the local ethics committees approved the study protocol prior to patient recruitment (Medical Research Ethics Committee Utrecht; 20-027/D and University Health Network Research Ethics Board Toronto; 21-5815). A data safety monitoring board (DSMB) was established to monitor the safety of the patients during the trial. Four patient representatives were engaged in the set-up phase of the trial to ensure the study's relevance and study procedures to their needs, and to ascertain that the patient information provided was clear and comprehensible. We adhered to the CONSORT guidelines for reporting randomised controlled trials.(1)

Participants

Inclusion took place between September 2020 and January 2023. Adult patients chronically using RASi as treatment of hypertension who were scheduled for elective, intermediate to high-risk non-cardiac surgery as defined by the European Society of Cardiology/European Society of Anaesthesiology Guideline on non-cardiac surgery, with an anticipated postoperative length of stay of at least two nights were eligible for

inclusion.(2) Eligible participants included patients using a combination pill of a RASi with a diuretic.

Exclusion criteria were severe chronic kidney disease, defined by a glomerular filtration rate (GFR) below 30 ml/min/1.73 m2; a history of chronic systolic heart failure with a left ventricular ejection fraction of ≤40%, including patients whose ejection fraction had improved to >40% due to heart failure treatment such as RASi use or chronic resynchronization therapy; RASi use within one year after ST-elevated myocardial infarction; using a combination pill of a RASi together with a drug other than diuretics (i.e. calcium channel blockers, beta-blockers, and neprilysin inhibitors); use of direct renin inhibitors (i.e. aliskiren); unable to self-manage chronic medication (e.g., using a medication box or pill dispenser); undergoing (partial) nephrectomy, pheochromocytoma surgery or transplant surgery; and previous enrolment in this trial. Because of a severe adverse event that was possibly due to hypertension in a patient undergoing carotid surgery who was randomized to discontinuation of RASi therapy early during the trial, from January 2021 patients undergoing carotid surgery (including carotid endarterectomy and carotid bypass surgery) were also excluded.

Patients were screened for eligibility after their visit to the preoperative assessment clinic. Eligible patients were verbally informed about the trial by research personnel and received a patient information letter.

Intervention

Patients who signed informed consent were randomised approximately one week before surgery. Patients assigned to temporarily discontinue RASi therapy were instructed not to take this medication on the evening before surgery, on the day of surgery, and on the first day after surgery. The attending surgeon and surgical floor nurses were instructed to discontinue RASi therapy on the day of surgery and on the first postoperative day. Resumption of RASi therapy was recommended on the second day after surgery or on the third day at the latest, at the discretion of the attending physician. If deemed necessary by the attending physician, for example in case of hypotension or severe hypertension, it was allowed to advance or delay resumption of RASi. Participants assigned to perioperative continuation of RASi and their care team were instructed to continue the RASi throughout the perioperative period, as per regular care. In this group, it was also allowed to deviate from these

instructions if deemed necessary by the attending physician, e.g. in case of hypotension or need of vasopressors.

Outcomes

The primary outcome was postoperative AKI as defined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines as an absolute increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours, or an increase in serum creatinine of ≥1.5 times compared to baseline, which was known or presumed to have occurred within the prior seven days. (3) Urine volumes were not used to assess AKI because this often is not available for postoperative patients. AKI was chosen a primary outcome because the kidney is vulnerable to injury resulting from poor tissue perfusion as provoked by perioperative factors including hypotension, and because it is a frequently occurring complication that can be measured easily.

Secondary outcomes were adherence to the protocol regarding perioperative continuation or discontinuation of RASi, perioperative hypotension (defined as a mean arterial pressure of <65mmHg for at least 10 minutes), and use of vasoactive drugs to maintain blood pressure. Other secondary outcomes were perioperative hypertension (defined as a mean arterial pressure >180mmHg systolic or >110mmHg diastolic), acute postoperative myocardial injury defined as an absolute postoperative increase in serum troponin of more than the upper limit of normal as compared to the preoperative value, congestive acute heart failure as diagnosed by the attending physician or cardiologist, postoperative delirium as diagnosed by the attending physician, and duration of hospital or nursing home stay. In addition, secondary outcomes at three months after surgery included kidney function, end-stage renal disease defined as renal disease necessitating dialysis or organ transplantation, major adverse cardiovascular complications (MACE; defined as myocardial infarction, coronary revascularization, heart failure, arrhythmia or stroke), and RASi adherence (i.e. intake of this medication as prescribed). Two patient-reported outcome measures were collected before surgery and at four weeks and three months after surgery: quality of life using the European Quality of Life Five Dimension (EQ-5D) questionnaire, and disability using the World Health Organization Disability Assessment Schedule (WHODAS 2.0).(4,5)

Sample size calculation

Based on previous studies in comparable populations and local retrospective data, we estimated the incidence of the primary outcome AKI at 10%. To detect a reduction in AKI incidence from 10% to 7% in the intervention group (discontinuing RASi), with a type 1 error rate of 0.05, a power of 80%, and accounting for a 10% loss to follow-up, a total of 3,200 patients were required (N=1,600 per arm).

Data collection

After obtaining informed consent, all data were recorded in the electronic data capture tool (Castor EDC, Amsterdam, The Netherlands). Patient characteristics, comorbidities, chronic medication usage and surgical characteristics were recorded before surgery. Blood samples to assess preoperative creatinine and troponin levels were collected upon admission before surgery. Creatinine was measured on the first and second postoperative days, and troponin on the first postoperative day. Data on medication adherence, blood pressure measurements and occurrence of postoperative complications were collected during hospital stay. After discharge, patients were requested to have their blood drawn for creatinine measurement during a visit to the hospital within three months following surgery. Patients were also requested to retain their empty RASi packaging from the time of discharge up to three months and to send these to the hospital in order to evaluate medication adherence.

Before surgery, patients were asked to complete two questionnaires, the WHODAS 2.0 12-item, and the EuroQoL 5D questionnaires. These questionnaires were repeated during follow-up at four weeks and three months postoperatively. At three months, additional questionnaires were sent to assess adverse events.

Analysis

The baseline characteristics of participants are presented using numbers and percentages, means with standard deviations (SD) or medians with interquartile ranges (IQR) where appropriate. Missing data were compared between the two groups and imputed using multiple imputation with predictive mean matching generating 5 datasets.

The primary outcome AKI was compared between groups using chi-square testing. Next, it was compared by multivariable logistic regression analysis of the imputed datasets, presenting the results as an odds ratio (OR) with a corresponding 95% confidence interval. Variables included

in the model were allocation group, ASA class (classification according to the American Society of Anaesthesiologists), age, sex, diabetes mellitus, preoperative creatinine, diuretic usage, and postoperative prescription of NSAIDs or COX inhibitors. Group assignment was according to the “intention-to-treat” principle. Additionally, in a sensitivity analysis the primary outcome was evaluated using a "per-protocol" analysis.

Secondary outcomes were compared between groups using chi-square testing. Next, outcomes were compared by multivariable linear regression, and logistic regression where appropriate, including the same variables that were used in the model for the primary outcome.

Disability was assessed by comparing the mean postoperative change in WHODAS 2.0 score as compared to the preoperative score between groups. In addition, this was compared by using the minimal clinically important difference in disability defined as an increase of 5% or more as compared to the preoperative baseline, by disability-free survival indicated by a WHODAS score below 16%, and by clinically significant disability defined as with a WHODAS score exceeding 35%.(6) For quality of life the median of the EQ-5D Visual Analog Scale (VAS) and a standardized EQ-5D index for the Dutch and Canadian population was compared between the two groups. In this, an approximation for the Canadian population was derived based on the standardized EQ-5D index for the United States of America.

Statistical analyses were performed in R statistics (Version 2024.09.1 – © 2020-10-10, R, Inc., for Windows).

Protocol changes and termination of the trial

During and following the COVID-19 pandemic and subsequent personnel shortages, a significant reduction in the number of surgical procedures was observed, and patients were discharged sooner to overcome shortage of available (staffed) hospital beds. In addition, surgeries were relocated to other hospitals. In order to increase the inclusion rate, the inclusion criteria were broadened during the trial. From September 2022, patients with an anticipated postoperative length of stay of one night also were eligible for inclusion. Still, the study eventually had to be terminated prematurely due to a continuing low inclusion rate. The decision to terminate the study was made by the steering committee after consulting with the DSMB and the grant provider, after multiple attempts to increase patient inclusions and a thorough evaluation of potential possibilities.

The termination had implications for achievement of the study objectives, and the data collected up to that point were analysed accordingly. Because of the small number of included patients, directly after termination of the study and before data analysis, postoperative kidney function loss was post hoc added as outcome parameter. This outcome was defined by the change in preoperative to postoperative creatinine, in order to study possible small changes in kidney function between the groups. Subgroup analyses were not performed and as the sample size reached was too small to show statistically significant differences in any of the outcomes, p-values were not reported.

RESULTS

A total of 3,146 patients using RASi underwent screening, of whom 2,613 met the inclusion criteria. 1,749 patients were excluded because of exclusion criteria, competing trials or for logistical reasons. Of 864 eligible patients, 342 patients were enrolled in the study (Figure 1). At the moment of early termination of the study, 318 patients had been randomised of which 305 had undergone surgery, i.e. 10% of the targeted sample size. Patients who were awaiting surgery or had not yet been randomised were informed about termination of the study and did not undergo the study intervention.

The majority of included patients were male (63%), and the median age was 68 (IQR 61-75) years. The predominant ACEi used was perindopril (32%), and the most commonly used ARB was losartan (40%) (Supplemental Table 1).

Primary outcome

Among the 305 patients, 288 patients (94%) had laboratory tests conducted on the first postoperative day, and 240 patients (79%) both on the first and second postoperative days. AKI occurred in seven patients (5%) in the continuation group and in five patients (3%) in the discontinuation group (RR 0.7, 95% CI 0.2-2.3) (Supplemental Table 2). Following multiple imputation of 4% missing values, multivariable logistic regression analysis showed no statistically significant effect of temporarily discontinuation of RASi therapy (OR 0.8, 95% CI 0.5-1.2). Men had a higher risk of developing AKI than women (OR 2.9, 95% CI 1.6-5.2) (Supplemental Table 3).

Secondary outcomes

No differences were observed in postoperative creatinine values and kidney function (Supplemental Table 2). None of the patients needed renal replacement therapy and no differences were found in other complications, admission duration, or discharge location between the groups. After three months of follow-up, none of the patients had developed kidney failure. In both groups, four patients experienced MACE.

None of the patients had hypotension before surgery (Supplemental Figure 1). Hypertension immediately before surgery was more common in the discontinuation group (25% versus 13%, RR 1.9, 95% CI 1.0-3.4). We observed no difference in the occurrence of intraoperative hypotension (19% in the group continuing RASi, and 17% in the discontinuation group, RR 0.9, 95% CI 0.5-1.6), nor in the duration of hypotension (14 vs 20 minutes, median difference 6 minutes). The incidence of intraoperative hypertension also was not different between groups (15% and 18%, RR 1.2, 95% CI 0.6-2.2). After surgery, hypotension occurred less often in the group of patients who discontinued their RASi (12% versus 4%, RR 0.3, 95% CI 0.1-0.9). We observed no difference in the occurrence of postoperative hypertension (11% versus 18%, RR 1.3, 95%-CI 0.7-2.3).

Quality of life and disability

The median EQ-5D and WHODAS scores were comparable at baseline. The 4-week follow-up survey was completed by 254 patients (83%), and the 3-month follow-up survey by 247 patients (81%). The median values of both the EQ-5D VAS and the EQ-5D index showed no differences between the two groups at four weeks and three months after surgery (Supplemental Table 4). The median WHODAS scores were also comparable between groups at four weeks and three months after surgery. A minimal clinically important difference of WHODAS ≥ 5% at three months postoperatively was noted in 46 patients (38%) in the group continuing RASi and 31 patients (26%) in the group temporarily discontinuing RASi therapy (RR 0.8, 95% CI 0.7-1.0). Disability-free survival at three months, defined as WHODAS <16%, was observed in 71 patients (58%) in the group continuing RASi, and in 66 patients (55%) in the group temporarily discontinuing RASi therapy (RR 1.0, 95% CI 0.7-1.3). No difference in clinically important disability, defined as WHODAS >35%, was found between the groups at three months (RR 1.0, 95% CI 0.9-1.1) (Supplemental Table 5).

Protocol adherence

Before surgery, 295 patients (97%) adhered to the protocol they were randomised to: 146 of 153 patients (95%) in the continuation group took the RASi, and 149 of 152 patients (98%) in the discontinuation group did not take this medication on the day of surgery. On the first postoperative day, among patients still hospitalized, protocol adherence was 80% for those in the continuation group and 88% for those in the discontinuation group. Notably, in most patients in the continuation group who did not receive RASi therapy, it was deliberately not administered due to hypotension. By the second postoperative day, 87% of patients in the continuation group who were still in the hospital received their RASi. In the discontinuation group, as the protocol recommended that the RASi should be resumed on the second or third postoperative day, 45% and 69% of patients received their RASi on the second and third postoperative day, respectively. On the fourth postoperative day, no difference in RASi administration between the continuation (80%) and discontinuation group (77%) was noted. At discharge, in 91% of patients the RASi was resumed as before surgery (Supplemental Table 6). Patients who did not resume their RASi as before, either were not hypertensive at the moment of discharge, received another dosage, or received another antihypertensive drug.

REFERENCES

1. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726–32.
2. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur Heart J. 2014;35(35):2383–431.
3. KDIGO Clinical Practice Guideline for Acute Kidney Injury. 2012;2(1). Available from: http://www.kidney-international.org
4. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011 Dec;20(10):1727–36.
5. Shulman MA, Myles PS, Chan MTV, McIlroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. Anesthesiology. 2015;122(3):524–36.
6. Shulman MA, Kasza J, Myles PS. Defining the Minimal Clinically Important Difference and Patient-acceptable Symptom State Score for Disability Assessment in Surgical Patients. Anesthesiology. 2020 Jun;132(6):1362–70.

S2. SUPPLEMENTARY TABLES AND FIGURES

Supplemental Table 1. Baseline characteristics

		Continue RASi N = 153	Discontinue RASi N = 152
Patient Characteristics			
Female sex, N (%)		54 (35)	59 (39)
Age in years, median (IQR)		67 (60-74)	68 (62-74)
BMI, median (IQR)		28 (25-31)	28 (25-31)
Medical history			
ASA classification, N (%)	ASA 1/2	51 (33)	64 (42)
	ASA 3/4	102 (67)	88 (58)
Hypertension, N (%)		153 (100)	152 (100)
Kidney disease, N (%)		19 (12)	21 (14)
Diabetes mellitus, N (%)		34 (22)	32 (21)
Stroke, N (%)		18 (12)	16 (11)
Peripheral vascular disease, N (%)		21 (14)	29 (19)
COPD, N (%)		16 (10)	29 (18)
Ischemic heart disease, N (%)		28 (18)	24 (16)
Atrial fibrillation, N (%)		26 (17)	27 (18)
Active malignancy, N (%)		63 (82)	56 (84)
Current smoker, N (%)		22 (14)	25 (17)
Preoperative medication use			
RASi, N (%)	ACEi	83 (54)	84 (55)
	ARB	70 (46)	68 (45)
	Combined with diuretic in one pill	22 (14)	12 (8)
Beta-blocker, N (%)		47 (31)	50 (33)
Calcium antagonist, N (%)		50 (33)	44 (29)
Diuretic, N (%)		33 (22)	46 (30)
NSAID or COXi		11 (7)	8 (5)
Surgery			
Surgical specialty, N (%)	General	38 (25)	27 (18)
	Neurosurgery	21 (14)	26 (17)
	Vascular	29 (19)	34 (22)
	ENT	11 (7)	8 (5)

Supplemental Table 1. Continued

		Continue RASi N = 153	**Discontinue RASi** N = 152
	Orthopedic	22 (14)	26 (17)
	Gynecology	14 (9)	9 (6)
	Urology	8 (5)	13 (9)
	Non-cardiac thoracic*	10 (7)	9 (6)
Center, N (%)	UMC Utrecht	85 (56)	83 (55)
	Erasmus MC Rotterdam	8 (5)	10 (7)
	Amsterdam UMC	31 (20)	30 (20)
	Antonius Hospital Nieuwegein	10 (7)	8 (5)
	Amphia Hospital Breda	15 (10)	17 (11)
	University Health Network Toronto	4 (3)	4 (3)

* lung and esophageal surgery

ASA, American Society of Anesthesiologists; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COXi, cyclooxygenase inhibitors; CVA, cerebrovascular accident; ENT, ear, nose, throat; Hb, hemoglobin; IQR, interquartile range; L, liter; MC, medical center; N, number; NSAID, non-steroidal anti-inflammatory drug; RASi, renin-angiotensin system inhibitors; UMC, university medical center

Supplemental Table 2. Outcomes in the continuation and discontinuation group

	Continue RASi N = 153	**Discontinue RASi** N = 152
In-hospital complications		
AKI, N (%) *	7 (5)	5 (3)
Change in kidney function (i.e. postoperative creatinine – preoperative creatinine), mean (±SD)	3.5 (±15.2)	4.4 (±20.6)
Renal replacement therapy, N (%)	0 (0)	0 (0)
Myocardial infarction, N (%)	0 (0)	0 (0)
Postoperative acute myocardial injury, N (%)	12 (9)	13 (9)
New arrhythmia, N (%)	4 (3)	6 (4)
CVA, N (%)	2 (1)	5 (3)
Delirium, N (%)	0 (0)	2 (1)
Reoperation, N (%)	4 (3)	5 (3)
Unexpected MC/ICU admission, N (%)	1 (1)	2 (1)
Admission and discharge		
Duration of hospital admission, median (IQR)	4 (2-7)	3 (2-7)
Discharge to rehabilitation center, nursing home or hospice care, N (%)	10 (7)	12 (8)
Complications at three months		
MACE, N (%)	4 (3)	4 (3)
End stage renal disease, N (%)	0 (0)	0 (0)
Change in kidney function (i.e. postadmission creatinine – preoperative creatinine), mean (±SD)	1.3 (±12.4)	2.8 (±15.1)

* According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines

AKI, acute kidney injury; CVA, cerebrovascular accident; COX, cyclooxygenase; ESC, European Society of Cardiology; ICU, intensive care unit; IQR, interquartile range; L, liter; MACE, Major Adverse Cardiovascular Events; MC, medium care; N, number; ng, nanogram; NSAID, non-steroidal anti-inflammatory drug; RASi, renin-angiotensin system inhibitors; RRT, renal replacement therapy

Supplemental Table 3. Regression analysis of the effect of discontinuing RASi on acute kidney injury and kidney function, adjusted for possible confounders and using the imputed dataset.

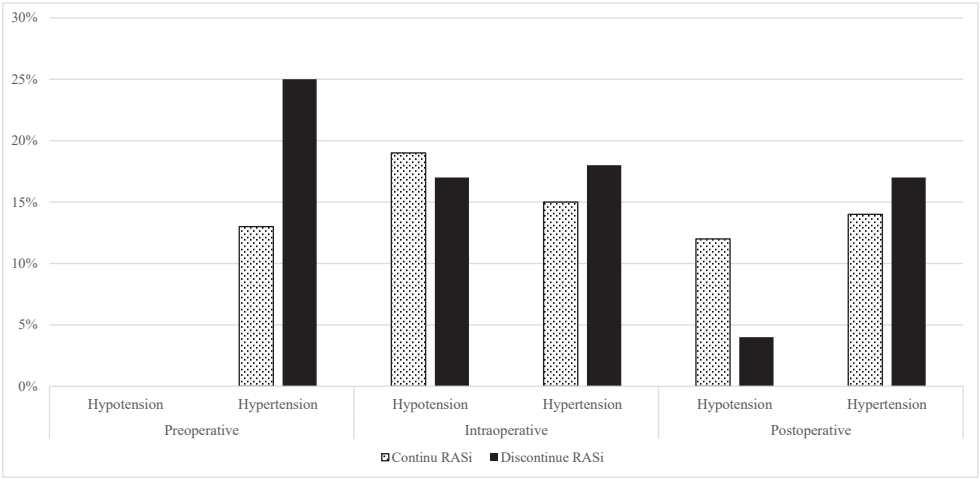
		OR	95% CI
AKI (intention to treat)	Perioperative RASi discontinuation	0.77	0.48 – 1.24
	ASA 3/4	0.95	0.57 – 1.56
	Age (per year increase)	1.01	0.98 – 1.04
	Male sex	2.85	1.55 – 5.24
	Diabetes mellitus	1.14	0.65 – 1.98
	Preoperative creatinine (per µmol/L increase)	0.99	0.98 – 1.00
	Chronic diuretic use	0.63	0.37 – 1.08
	Postoperative administration of NSAID/COXi	0.95	0.58 – 1.56
AKI (per protocol analysis)	Perioperative RASi discontinuation	0.98	0.97 – 0.99
	ASA 3/4	1.04	0.63 – 1.72
	Age	1.01	0.98 – 1.04
	Male sex	2.93	1.58 – 5.45
	Diabetes mellitus	1.03	0.59 – 1.82
	Preoperative creatinine (per µmol/L increase)	0.99	0.98 – 1.00
	Chronic diuretic use	0.61	0.36 – 1.05
	Postoperative administration of NSAID/COXi	0.94	0.57 – 1.53
		Regression coefficient	**95% CI**
Postoperative creatinine	Perioperative RASi discontinuation	0.65	-0.99 – 2.30
	ASA 3/4	-0.90	-2.61 – 0.81
	Age	0.20	0.10 – 0.28
	Male sex	5.55	3.71 – 7.38
	Diabetes mellitus	2.25	0.26 – 4.25
	Preoperative creatinine (per µmol/L increase)	-0.11	-0.14 – -0.07
	Chronic diuretic use	0.11	-1.61 – 1.83
	Postoperative administration of NSAIDs/COXi	-2.13	-3.85 – -0.42

Supplemental Table 3. Continued

		OR	95% CI
Postadmission creatinine	Perioperative RASi discontinuation	1.21	-0.08 – 2.51
	ASA 3/4	-1.23	-2.58 – 0.12
	Age	0.06	-0.01 – 0.14
	Gender male	3.87	2.42 – 5.32
	Diabetes mellitus	-1.78	-3.35 - -0.21
	Preoperative creatinine (per µmol/L increase)	-0.078	-0.11 - -0.05
	Chronic diuretic use	2.88	1.52 – 4.23
	Postoperative administration of NSAID/COXi	-1.59	-2.95 - -0.24

AKI, acute kidney injury; ASA, American Society of Anesthesiologists; CI, confidence interval; COXi, cyclooxygenase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drug; OR, odds ratio; RASi, Renin-Angiotensin System Inhibitors

Supplemental Figure 1. Incidence of perioperative hypotension and hypertension in continuation and discontinuation group



Abbreviations: RASi, Renin-Angiotensin System Inhibitors

Supplemental Table 4. Quality of life before and after surgery in the continuation and discontinuation group

QoL measure		Continue RASi	Participants	Discontinue RASi	Participants
EQ-5D VAS	Preoperative	75 (58-85)	N = 151	70 (55-80)	N = 147
	4 weeks postoperative	70 (53-80)	N = 129	70 (70-80)	N = 125
	3 months postoperative	71 (60-85)	N = 127	75 (60-85)	N = 120
EQ-5D index value	Preoperative	0.81 (0.61-0.88)	N = 329	0.78 (0.55-0.88)	N = 329
	4 weeks postoperative	0.74 (0.61-0.87)	N = 288	0.78 (0.61-0.84)	N = 288
	3 months postoperative	0.80 (0.69-0.91)	N = 282	0.80 (0.69-0.88)	N = 282

EQ-5D, European Quality of Life Five Dimension; IQR, interquartile range; N, number; QoL, quality of life; RASi, Renin-Angiotensin System Inhibitors; VAS, visual analog scale

Supplemental Table 5. Disability (as measured by the WHODAS questionnaire) before and after surgery in the continuation and discontinuation group

Disability measure		Total N	Continue RASi		Discontinue RASi	
			Median (IQR)	N*	Median (IQR)	N*
WHODAS %	Preoperative	287	8.3 (2.1-26.0)	143	12.5 (4.2-32.3)	143
	4 weeks postoperative	253	20.8 (10.4-35.4)	129	20.8 (10.4-37.5)	124
	3 months postoperative	242	10.4 (4.2-27.1)	123	12.5 (6.3-27.1)	119
			Mean (±SD)		Mean (±SD)	
WHODAS % change	3 months postoperative compared to preoperative	240	0.3 (±16.4)	121	-2.3 (±18.4)	119
			N (%)		N (%)	
Minimal clinically important difference (increase ≥5%)	3 months postoperative compared to preoperative	240	46 (38%)	121	31 (26%)	119
Disability free survival (WHODAS <16%)	3 months postoperative	242	71 (58%)	123	66 (55%)	119
Clinically important disability (WHODAS >35%)	Preoperative	286	90 (63%)	143	76 (53%)	143
	3 months postoperative	242	71 (58%)	123	66 (55%)	119

*Number of patients with completed WHODAS 2.0 questionnaire

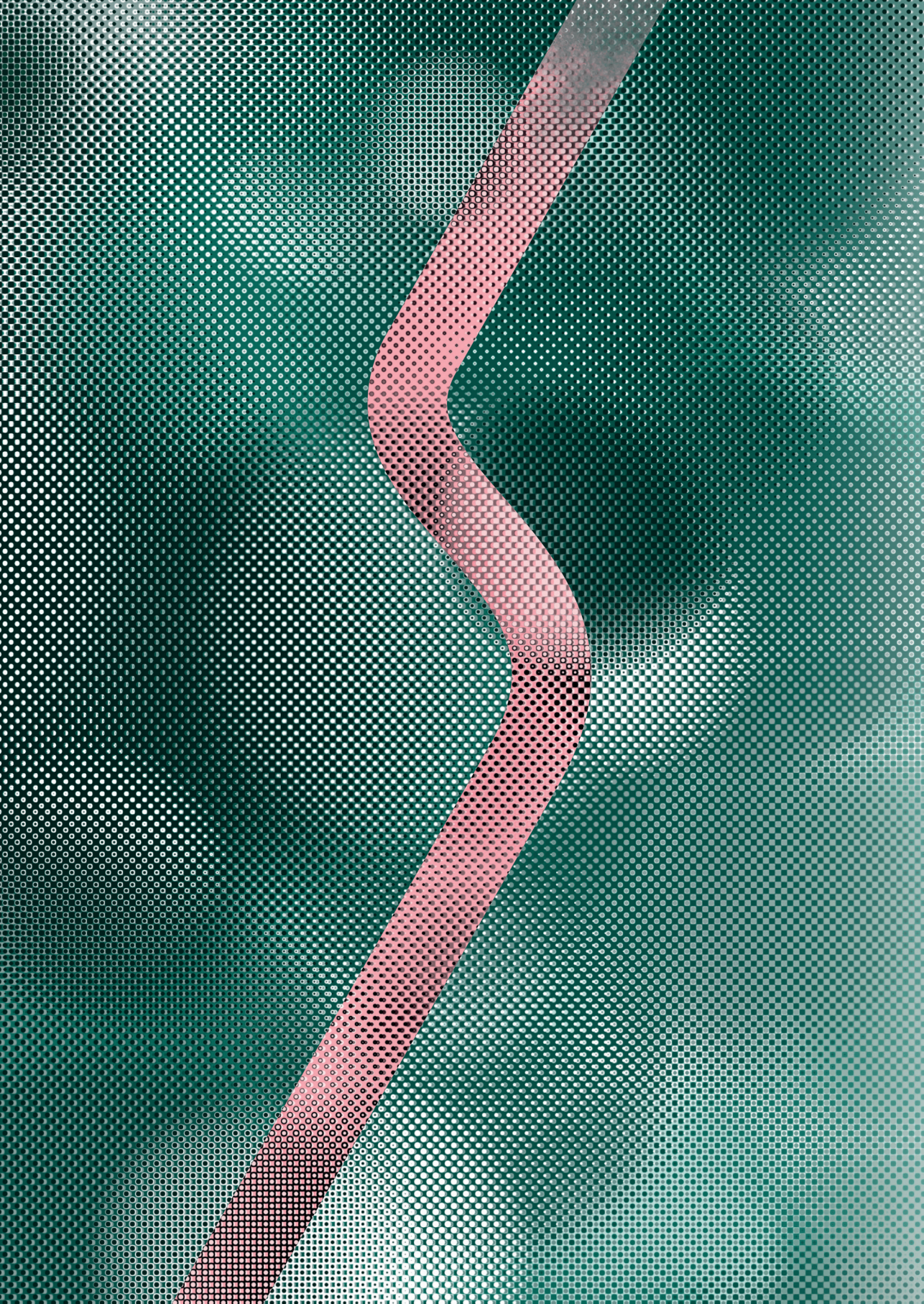
IQR, interquartile range; N, number; RASi, renin-angiotensin system inhibitors; SD, standard deviation; WHODAS, World Health Organization Disability Assessment Score

Supplemental Table 6. Adherence to the medication instructions in the continuation and discontinuation group

		Continue RASi N = 153	**Discontinue RASi** N = 152
RASi taken within 24 hours before surgery, N (%)		146 (95)	3 (2)
RASi administered during hospital admission*, N (%)	Postoperative day 1	118 (80)	18 (12)
	Postoperative day 2	112 (87)	59 (45)
	Postoperative day 3	91 (88)	70 (69)
	Postoperative day 4	63 (80)	55 (77)
RASi prescribed at discharge, N (%)		139 (91)	138 (93)

* Of patients still admitted to the hospital.

Abbreviations: N, number; RASi, Renin-Angiotensin System Inhibitors



CHAPTER 4

Adherence to medication intake instructions before surgery in patients taking renin-angiotensin system inhibitors.

Judith A.R. van Waes (1), Lynn A. Miggelbrink (1), Kim C.M. van der Elst (2), Erin H. Smeijsters (2), Wilton A. van Klei (1)

Departments of 1. Anaesthesiology, 2. Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, the Netherlands.

Accepted for publication (in press), British Journal of Anaesthesia
Available as preprint (Br J Anaesth. 2026 Sep 21:S0007-0912(26)00619-7. doi: 10.1016/j.bja.2026.07.052

EDITOR,

Recently, several randomized clinical trials have addressed whether renin angiotensin system inhibitors (RASi) should be continued or discontinued before major elective non-cardiac surgery.(1–4) A meta-analysis including these trials showed no difference in cardiovascular complications, acute kidney injury, and death between patients continuing or withholding RASi around surgery.(5) An important topic not studied in these trials, was adherence to chronic cardiovascular medications such as RASi. When implementing results of these trials in clinical care, it should be noted that adherence to chronic cardiovascular medications is generally poor (57%).(6) Likewise, before elective surgery, adherence to preoperative medication instructions has been shown to be around 72%.(7,8) In these studies, adherence was measured using patient interviews, and as this method may be subject to response bias, true medication adherence around surgery remains unknown. We therefore aimed to study medication adherence by measuring plasma concentrations of RASi on the day of surgery in patients who were instructed to either continue or discontinue this medication before surgery. Secondary, we aimed to compare hemodynamic parameters, and the need for vasopressors, inotropes, or fluids during surgery between patients who had continued and discontinued RASi.

This was a sub study of the AIPOP trial, a randomized controlled trial comparing temporary discontinuation versus continuation of RASi (NCT04506372).(3) All participants provided written informed consent and the local ethics committees approved the study protocol prior to patient recruitment (Medical Research Ethics Committee Utrecht; 20-027/D). Eligible patients were those using RASi for treatment of hypertension and undergoing major non-cardiac surgery at the University Medical Center Utrecht, The Netherlands. Patients using candesartan were excluded from this sub study because plasma concentration measurements were not available for this drug. Patients were randomised to temporarily discontinue RASi therapy one day before surgery, or to continue the drug throughout the perioperative period. Within one week before surgery, participants received verbal instructions by telephone to either continue or discontinue RASi and received a paper diary to document their actual medication use around surgery.

The primary outcome was adherence to the preoperative instructions based on RASi serum measurements. Blood samples were collected

in the operating theatre prior to the start of surgery. RASi plasma concentrations were measured using a validated LC-MS/MS method.(9) For each participant, two independent clinical pharmacists, blinded to group allocation, individually assessed, whether RASi was surely taken, probably taken, or probably not taken before surgery, or if adherence before surgery was too ambiguous to determine. In this assessment, measured RASi plasma concentrations were compared with expected mean through concentrations, derived from reference populations from previous clinical trials or registration trails of the specific RASi, to establish a concentration ratio for each drug. The evaluation considered the pharmacokinetics of the drug (time to peak plasma concentration, half-life), the prescribed dosage relative to the reference population, and the interval between intended intake and blood sampling. After completing their individual assessments, the two pharmacists jointly reviewed all cases to reach consensus.

Patients were classified as adherent to the preoperative instructions if RASi was (probably) taken in the continuation group, or probably not taken in the discontinuation group. RASi concentration ratios were compared between groups using Mann-Whitney U testing, and the proportion of adherent patients were compared using Chi-square testing. Blood pressures, and the need for vasopressors, inotropes, and fluids were compared between groups and between patients who (probably) continued and those who probably discontinued RASi before surgery.

Between December 2021 and January 2023, 50 patients were included. Four patients using candesartan were excluded, resulting in 24 patients in the RASi continuation group and 22 in the discontinuation group. Their mean age was 68 years (SD 7), and 72% was male. The most used RASi drugs were losartan, lisinopril and perindopril (Supplemental Table 1). According to the patient medication diaries, RASi was taken according to preoperative instructions in 23 patients (96%) in the continuation group and withheld in 22 patients (100%) in the discontinuation group (Table 1). The median RASi concentration ratio was 12 (range 0-327) in the continuation group and 4 (range 0-58) in the discontinuation group (p=0.094). According to blinded pharmacist adjudication, RASi was (probably) taken in 18 patients (75%) in the continuation group and in 11 patients (60%) in the discontinuation group. RASi was probably not taken in 3 patients (13%) in the continuation group and in 6 patients (27%) in the discontinuation group (Table 1). The two blinded pharmacists independently arrived at the same conclusion in 44 of 46 participants, and

in the remaining two cases consensus was achieved through discussion. Based on these numbers, adherence to the medication instructions as provided before surgery was 75% in the continuation group versus 27% in the discontinuation group (RR 2.8, 95% CI 1.3-5.7, p=0.001).

Table 1. Preoperative intake of RASi

	Continue RASi N=24 (%)	**Discontinue RASi** N=22 (%)
Taken before surgery according to diary	23 (95.8)	0 (0)
Median concentration ratio of RASi before surgery (range)	12 (0-327)	4 (0-58)
Interpretation of RASi serum measurement		
Taken	15 (62.5)	6 (27.3)
Probably taken	3 (12.5)	5 (22.7)
Probably not taken	3 (12.5)	6 (27.3)
Unsure	3 (12.5)	5 (22.7)
Likely adhered to preoperative instructions	18 (75.0)	6 (27.3)

RASi: renin angiotensin system inhibitors

No differences in hemodynamic parameters and need for vasopressors or inotropes were found between the two groups. When comparing hemodynamic parameters between patients who had (probably) taken RASi to patients who had probably not taken RASi, no differences were found (Supplemental Table 2).

The overall adherence rate to instructions about RASi (dis)continuation of 52% in this study are in line with previous reports about adherence to chronic medications.(6–8) In recent trials however, higher adherence rates were reported. In the Stop-Or-Not trial, overall adherence to RASi intake was 96%, which is comparable to our study when adherence was based solely on medication diaries.(1) In the POISE-3 and SPACE trials, adherence to RASi intake was higher in the discontinuation group (95% and 98% respectively) than in the continuation group (38% and 88% respectively). However, because drug intake was not confirmed by drug concentration measurements, this may not reflect true adherence.(2,4)

In our study we found a large range in RASi plasma concentration ratios between individual patients, including within both groups. This may reflect (non)adherence to instructions, but most likely also resulted from differences in pharmacokinetics. As the half-lives of RASi drugs in our

study ranged between 6 and 20 hours, discontinuing RASi on the morning of surgery will not always result in low plasma concentrations by the time of surgery. However, even when the duration of RASi cessation was based on the specific pharmacokinetics of each drug, as was done in the SPACE trial, no difference in adverse outcomes was observed.(2) In a sub study of this trial, it was shown that effective RAAS inhibition was associated with adverse outcomes, rather than either continuation or discontinuation of RASi.(10)

In conclusion, we found that 52% of patients did not adhere to written and verbal instructions regarding (dis)continuation of RASi before surgery. Given the lower adherence rates in the discontinuation group as found in this study and the need for different cessation times between RASi drugs, together with the results from recent trials showing no benefit of discontinuation of RASi over continuation, it may be considered most appropriate to advise patients to continue RASi before surgery.

REFERENCES

1. Legrand M, Falcone J, Cholley B, Charbonneau H, Delaporte A, Lemoine A, et al. Continuation vs Discontinuation of Renin-Angiotensin System Inhibitors Before Major Noncardiac Surgery. JAMA. 2024 Sep 24;332(12):970. doi:10.1001/jama.2024.17123
2. Ackland GL, Patel A, Abbott TEF, Begum S, Dias P, Crane DR, et al. Discontinuation vs. continuation of renin–angiotensin system inhibition before non-cardiac surgery: the SPACE trial. Eur Heart J. 2024 Apr 1;45(13):1146–55. doi:10.1093/eurheartj/ehad716
3. Miggelbrink LA, van Klei WA, Verhaar MC, Asselbergs FW, Spiering W, Buhre WFFA, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the perioperative period: withdraw or continue? A multicentre randomised controlled trial. British Journal of Anaesthesia. Elsevier Ltd; 2025. p. 1075–7. doi:10.1016/j.bja.2025.05.056 PubMed PMID: 40701887.
4. Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, Chan MTV, et al. Hypotension-Avoidance Versus Hypertension-Avoidance Strategies in Noncardiac Surgery. Ann Intern Med. 2023 May;176(5):605–14. doi:10.7326/M22-3157
5. Shalabi L, Ibrahim A, Zreigh S, Rifai M, Ramadan S, Arafa MA, et al. Evaluating the risks and benefits of continuing versus withholding renin–angiotensin system inhibitors: a systematic review and meta-analysis with trial sequential analysis. BJA Open. 2025 Jun;14:100405. doi:10.1016/j.bjao.2025.100405
6. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: Meta-analysis on 376,162 patients. American Journal of Medicine. 2012;125(9):882-887.e1. doi:10.1016/j.amjmed.2011.12.013
7. Van Waes JAR, De Graaff JC, Egberts ACG, Van Klei WA. Medication discontinuity errors in the perioperative period. Acta Anaesthesiol Scand. 2010 Nov;54(10):1185–91. doi:10.1111/j.1399-6576.2010.02318.x PubMed PMID: 21039342.
8. Clifton J, McIlroy D, Henson CP, Freundlich R. Improving quality of medication management by investigating compliance to preoperative ACE inhibitor and ARB medication instructions. Br J Anaesth. 2025 Jul;135(1):251–3. doi:10.1016/j.bja.2025.04.023
9. Punt AM, Stienstra NA, van Kleef MEA, Lafeber M, Spiering W, Blankestijn PJ, et al. Screening of cardiovascular agents in plasma with LC-MS/MS: A valuable tool for objective drug adherence assessment. J Chromatogr B Analyt Technol Biomed Life Sci. 2019 Jul 15;1121:103–10. doi:10.1016/j.jchromb.2019.05.013 PubMed PMID: 31146083.
10. Gutierrez del Arroyo A, Abbott TEF, Patel A, Begum S, Dias P, Brealey D, et al. Preoperative activation of the renin–angiotensin system and myocardial injury in noncardiac surgery: exploratory mechanistic analysis of the SPACE randomised controlled trial. Br J Anaesth. 2024. doi:10.1016/j.bja.2024.10.040

SUPPLEMENTARY FILES

S1. Baseline characteristics

	All patients N=46	Continue RASi N=24 (%)	Discontinue RASi N=22 (%)
Mean age (SD)	68.3 (7.1)	69.4 (7.0)	67.1 (7.2)
Male sex	33 (71.7)	16 (66.7)	17 (77.3)
Mean BMI (SD)	27.9 (5.8)	26.2 (3.7)	29.6 (7.0)
ASA class 3/4	30 (65.2)	17 (70.8)	13 (59.1)
Hypertension	46 (100)	24 (100)	22 (100)
Ischemic heart disease	7 (15.2)	2 (8.3)	5 (22.7)
Diabetes mellitus	6 (13.0)	2 (8.3)	4 (18.2)
Chronic kidney disease	1 (2.2)	0 (0)	1 (4.5)
Mean preoperative eGFR (ml/min/1.73m^2)	76.6 (15.5)	76.9 (15.9)	76.3 (15.5)
RASi			
Losartan	9 (19.6)	4 (16.7)	5 (22.7)
Lisinopril	7 (15.2)	3 (12.5)	4 (18.2)
Perindopril	7 (15.2)	5 (20.8)	2 (9.1)
Irbesartan	6 (13.0)	3 (12.5)	3 (13.6)
Enalapril	5 (10.9)	3 (12.5)	2 (9.1)
Fosinopril	3 (6.5)	2 (8.3)	1 (4.5)
Olmesartan	3 (6.5)	0 (0)	3 (13.6)
Ramipril	2 (4.3)	1 (4.2)	1 (4.5)
Telmisartan	2 (4.3)	2 (8.3)	0 (0)
Valsartan	2 (4.3)	1 (4.2)	1 (4.5)
Beta blocker	15 (32.6)	6 (25.0)	9 (40.9)
Calcium channel blocker	13 (28.3)	5 (20.8)	8 (36.4)
Diuretic	14 (30.4)	5 (20.8)	9 (40.9)

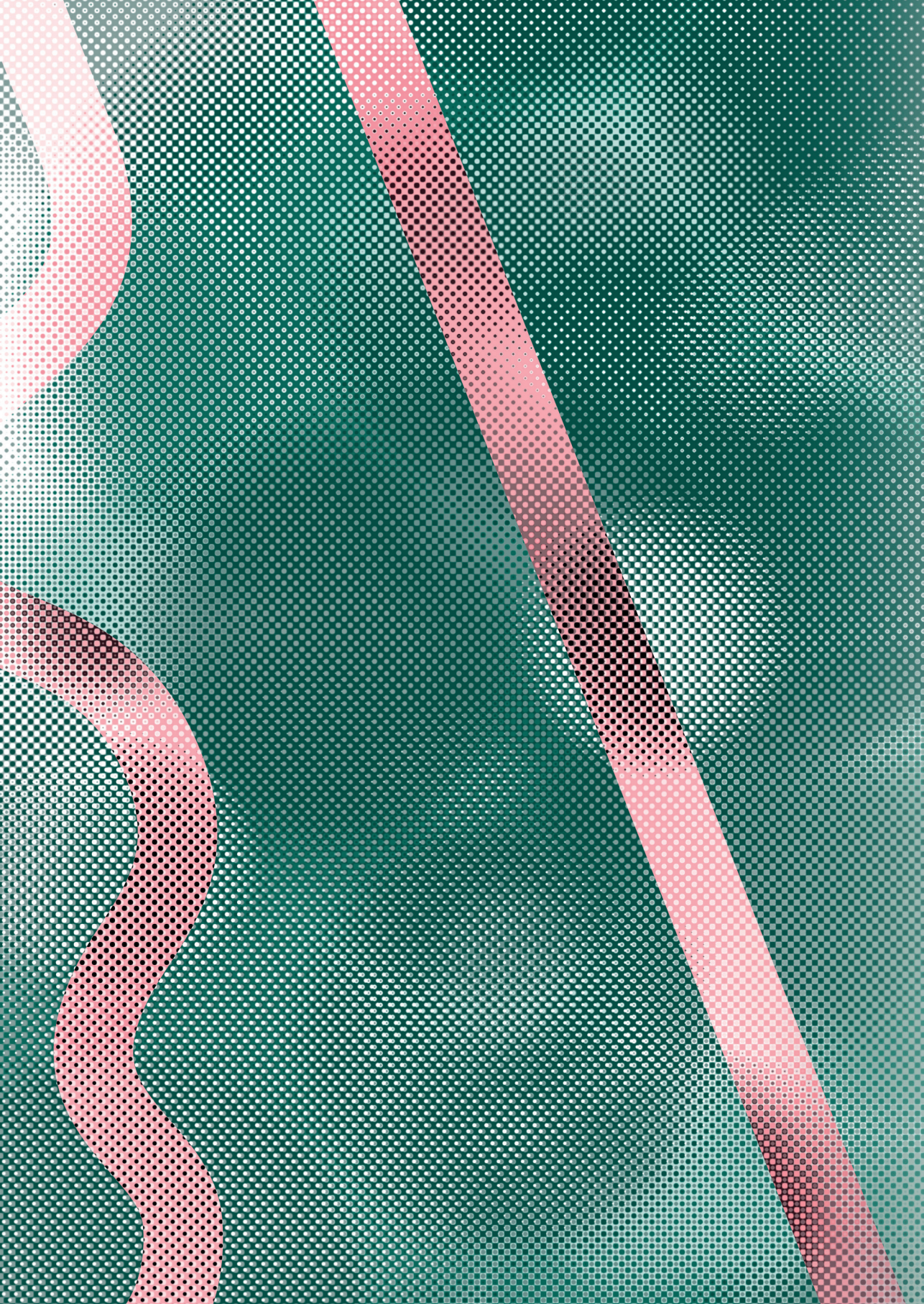
RASi: renin angiotensin system inhibitors; SD: standard deviation; BMI: body mass index;

ASA: American Society of Anesthesiology; eGFR: estimated glomerular filtration rate.

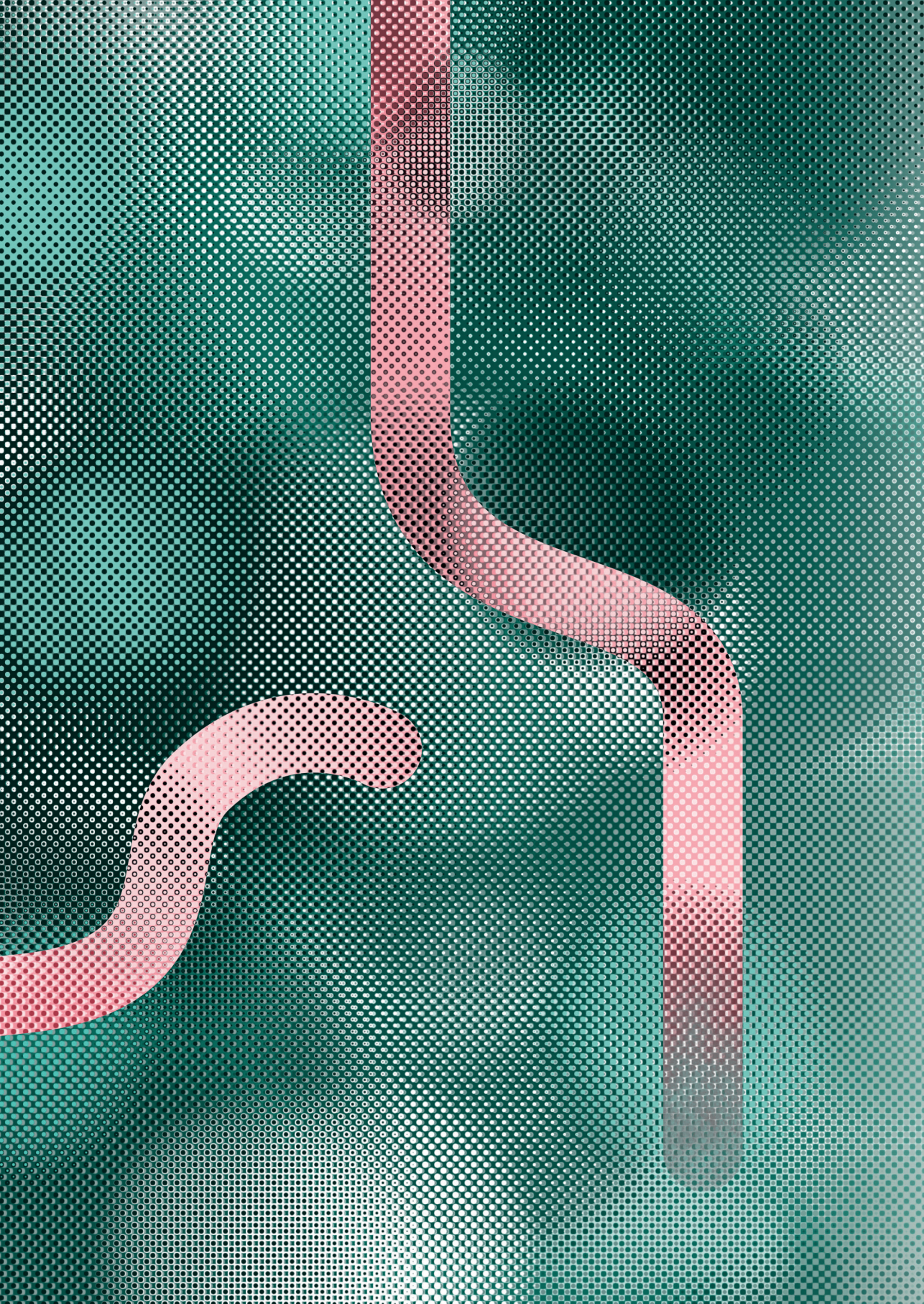
S2. Blood pressures and use of vasopressors and inotropes.

	Randomized to continue RASi N = 24 (%)	Randomized to discontinue RASi N = 22 (%)	RASi (probably) continued according to plasma measurement N = 29 (%)	RASi (probably) discontinued according to plasma measurement N = 9 (%)
Median surgery duration (minutes, IQR)	172 (137-294)	175 (126-247)	169 (124-277)	175 (127-237)
Mean MAP before induction (mmHg, SD)	115 (16)	114 (13)	112 (15)	114 (9)
Mean MAP during surgery (mmHg, SD)	86 (8)	86 (7)	86 (9)	87 (6)
Median number of minutes with MAP<65 mmHg (IQR)	2 (0-12)	0 (0-7)	1 (0-5)	4 (0-8)
Median amount of fluid (ml, IQR)	2000 (1513-4000)	3000 (2000-3250)	2000 (2000-4000)	2000 (1250-3500)
Received norepinephrine	4 (16.7)	0 (0)	2 (6.9)	0 (0)
Median amount of norepinephrine (mcg, range)	0 (0-70)	0 (0-0)	0 (0-20)	0 (0-0)
Received phenylephrine	11 (45.8)	11 (50.0)	10 (34.5)	7 (77.8)
Median amount of phenylephrine (mcg, range)	0 (0-930)	0 (0-400)	0 (0-930)	200 (0-500)
Received ephedrine	15 (62.5)	13 (59.1)	17 (58.6)	6 (66.7)
Median amount of ephedrine (mg, range)	5.0 (0.0-25.0)	6.3 (0.0-20.0)	5.0 (0.0-25.0)	5.0 (0.0-20.0)

RASi: renin angiotensin system inhibitors; IQR: inter quartile range; MAP: mean arterial pressure; SD: standard deviation.



PART II
INTRAOPERATIVE CORTICOSTEROID ADMINISTRATION



CHAPTER 5

Peri-operative corticosteroid supplementation guideline adherence.

Lynn A. Miggelbrink (1), Marije Marsman (1), Juul van de Wetering (1), Wendela L. de Ranitz-Greven (2), Judith A.R. van Waes (1), Wilton A. van Klei (1,3,4), Teus H. Kappen (1)

Department of 1. Anaesthesiology, 2. Endocrinology, UMC Utrecht, Utrecht, The Netherlands
Department of 3. Anaesthesiology, UHN Toronto, Toronto, Canada
Department of 4. Anaesthesiology, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada

Published as Science Letter
Anaesthesia. 2025 Apr;80(4):454-455. doi: 10.1111/anae.16556. Epub 2025 Jan 30.

DEAR EDITOR,

Corticosteroids are prescribed commonly to patients with autoimmune or pulmonary diseases, post-transplant and neurosurgery, as well as to patients with adrenal insufficiency.(1,2) These patients are at risk of tertiary adrenal gland insufficiency, for which supplementation of corticosteroids during stress, such as surgery, is advised.(3,4) The Peri-operative Replacement of Exogenous Steroids (PREdS) study performed an audit of compliance to guidelines for supplemental corticosteroids in patients with possible adrenal insufficiency in the UK.(5) A total of 21,411 adult patients undergoing surgery under the care of an anaesthetist were screened, of whom 277 (1.3%) used corticosteroids (i.e. they were considered at risk of tertiary adrenal gland insufficiency). Peri-operative prescription of supplementation was fully compliant in only 9% of the patients and 14% received none.

In a retrospective cohort study, we investigated guideline adherence for such patients in our academic centre. The local clinical guideline is based on a Dutch nationwide guideline, comparable with the one used in the UK (Table 1). Patients are deemed at risk if they are using prednisolone ≥ 7.5 mg or equivalent. Supplementation dosage depends on surgical risk, so we documented compliance based on a patient's surgical procedure risk.

A total of 15,246 patients undergoing elective non-cardiac surgery under general or spinal anaesthesia between January 2017 and June 2018 were included, of whom 390 were at risk of tertiary adrenal gland- insufficiency. Patients had a median age of 56 (45-69 [range 18-85]), 178 (45%) were female and 107 (27%) were scheduled for neurosurgery. On the day of surgery, 32 of 390 patients (8%) received hydrocortisone supplementation in accordance with the guidelines and 188 (48%) received another corticosteroid for an alternative reason, e.g. dexamethasone for postoperative nausea or for neurosurgery. None of the remaining 170 (44%) patients received supplementation.

Of the 147 patients (38%) undergoing low-risk surgery, 26 (18%) received supplementation according to the guidelines, while 38 (36%) received corticosteroids for other reasons, of whom 36 (95%) received an adequate equivalent dose. Of the 243 patients (62%) undergoing intermediate/high-risk surgery, 6 (2%) received supplemental corticosteroids according to the guidelines and 150 (62%) received corticosteroids for other reasons. Of these 150 patients, 27 (18%) received

an adequate equivalent dose. On the first postoperative day, peri-operative prescription of supplementation was fully compliant in 10 (4%) of the 243 intermediate/high-risk patients.

In conclusion, our hospital recorded an 8% compliance rate with the guidelines for prescribing peri-operative corticosteroid supplementation, similar to the 9% compliance rate found in the PREDs study [5]. Our study predates the Association of Anaesthetists' guidelines, yet the results indicate that peri-operative corticosteroid supplementation for chronic users remains controversial (6). Despite over 60 years of recommendations, these guidelines are based on sparse, low-quality evidence and need further scrutiny.

Table 1. Corticosteroid supplementation guidelines

Type of surgery*	Pre-operative	Postoperative		
	Day of surgery	Day 1	Day 2	Day 3
Low-risk	100 mg hydrocortisone i.v. or i.m. 1 h before surgery	n/a	n/a	n/a
Intermediate/high-risk	100 mg hydrocortisone i.v. or i.m. 1 h before surgery	3 x 40 mg hydrocortisone orally or 3 x 50 mg hydrocortisone i.v. or i.m.	1 x 40 mg and 2 x 20mg hydrocortisone orally	3 x 20 mg hydrocortisone orally
	100 mg hydrocortisone i.v. during induction			Taper to pre-operative dose
	2 x 50 mg hydrocortisone i.v. or i.m with a 6-h interval			

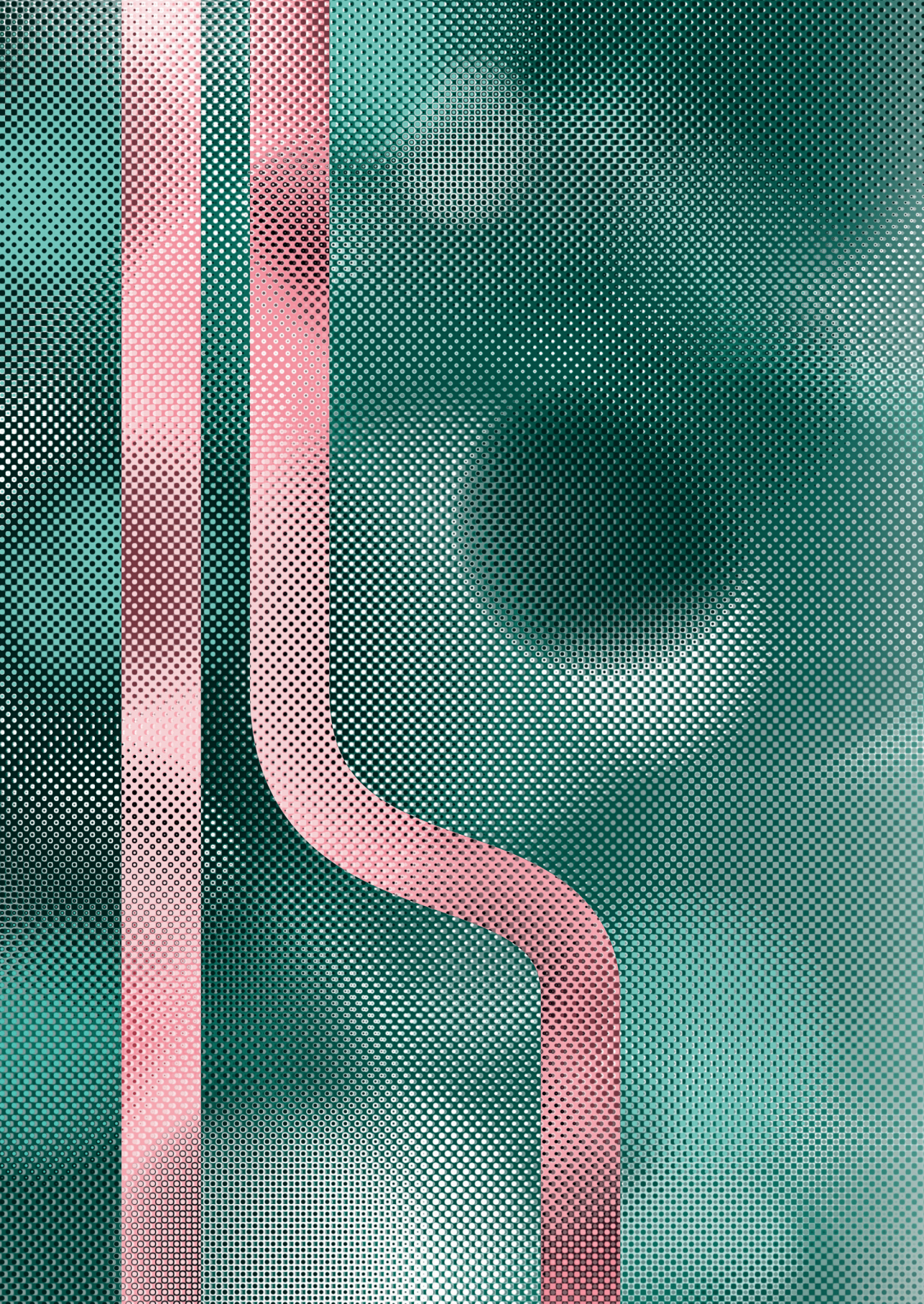
i.v., intravenous; i.m., intramuscular; n/a, not applicable.

*The dosages of this local translation of the national guidelines, are the same for all patients with continuation of the pre-operative corticosteroids. The local guideline was implemented in August 2013, and the latest update was February 2019.

REFERENCES

1. Coursin DB, Wood KE. Corticosteroid Supplementation for Adrenal Insufficiency. Vol. 287. 2013;287(2):236–40.
2. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – A systematic review. Dan Med J. 2018;65(6):1–5. PubMed PMID: 29886882.
3. Chilkoti G, Singh A, Mohta M, Saxena A. Perioperative 'stress dose' of corticosteroid: Pharmacological and clinical perspective. Journal of Anaesthesiology Clinical Pharmacology. 2019. doi:10.4103/joacp.JOACP_242_17
4. T. Woodcock, P. Barker, S. Daniel, S. Fletcher, J. A. H. Wass, J. W. Tomlinson, U. Misra, M. Dattani, W. Arlt AV. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency. Anaesthesia. 2020.
5. Barker OJH, Ramesh A V., Kangesan I, Barnes J, Harrogate S, Gupta S, et al. Peri-operative Replacement of Exogenous Steroids (PREdS): a national audit of current peri-operative prescribing for patients taking therapeutic steroids. Anaesthesia. 2024 Oct 3;79(10):1042–52. doi:10.1111/anae.16388
6. Woodcock T, Barker P, Daniel S, Fletcher S, Wass JAH, Tomlinson JW, et al. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency. Anaesthesia. 2020 May 3;75(5):654–63. doi:10.1111/anae.14963

Chapter 5



CHAPTER 6

Effects of a supra-physiological corticosteroid regime in surgical patients at risk for tertiary adrenal insufficiency, a retrospective cohort study.

L.A. Miggelbrink (1), H.B. Vroom (1), C.E. de Keyser (2), T.H. Kappen (1), W.A. van Klei (1,3,4,5), J.A.R. van Waes (1)

Department of 1. Anesthesiology, 2. Endocrinology, UMC Utrecht, Utrecht, The Netherlands

Department of 3. Anaesthesiology and Pain Management, Toronto General Hospital, University Health Network Toronto, Ontario, Canada.

Department of 4. Anaesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

Department of 5. Anaesthesiology and Pain Management, Toronto General Hospital Research Institute, Toronto, Ontario, Canada.

Not published, manuscript

ABSTRACT

Background: Patients who chronically use corticosteroids are at risk for tertiary adrenal gland insufficiency. Guidelines advise a supra-physiological stress dosages of corticosteroids in the perioperative period in patients at risk. However, evidence supporting this strategy is weak, and adherence to the guidelines low.

Methods: This retrospective single-center study included patients at risk for a tertiary adrenal gland insufficiency who underwent elective non-cardiac surgery between January 2017 and June 2018 at the University Medical Center in Utrecht. According to guidelines, these patients should receive stress-dose corticosteroids. Patients were divided into three groups: (1) stress-dose administered according to protocol, (2) additional non-equivalent doses of corticosteroids administered, (3) no corticosteroid administered in addition to the normal daily dose. Postoperative symptoms of adrenal gland insufficiency were compared between these groups using regression analysis with propensity score matching.

Results: 390 patients were at risk for tertiary adrenal gland insufficiency. Of those, 94 patients (24%) received corticosteroid stress-dose according to protocol, 125 patients (32%) received a non-equivalent dose, and 171 patients (44%) did not receive additional corticosteroids. Compared to patients who received no additional corticosteroids, neither treatment with an adequate corticosteroid stress-dose, nor treatment with a non-equivalent corticosteroid dosage was associated with postoperative symptoms during the first three postoperative days (OR 1.5, 95% CI 0.5-4.0 and OR 1.4, 95% CI 0.5-3.5, respectively).

Conclusion: This retrospective study showed no difference in postoperative symptoms in patients at risk for tertiary adrenal gland insufficiency who did or did not receive a supra-physiological stress-dose of corticosteroids.

Key words: stress-dose, corticosteroids, tertiary adrenal gland insufficiency, steroid induced adrenal gland insufficiency, perioperative, surgery

INTRODUCTION

Cortisol is a glucocorticoid hormone produced by the adrenal glands. Normal cortisol secretion for adults is 8-10 mg/day, increasing to 50 mg/day under minor stress such as illness, and returning to baseline values after approximately 24 hours.(1,2) In case of extreme stress (e.g., major surgery), cortisol secretion can increase to 75-150 mg/day and returns to normal after approximately 5 days.(3,4) Exogenous glucocorticoids are commonly prescribed for treatment of autoimmune, inflammatory and pulmonary diseases.(5,6) It has been reported that chronic corticosteroid usage could suppress the hypothalamic-pituitary-adrenal axis. Early, non-specific symptoms of such adrenal insufficiency include fatigue, muscle aches, loss of appetite, nausea and vomiting.(7), More severe symptoms reported around surgery include hemodynamic instability.(8) In the 1950's, even a few cases of patients who unexpectedly died during surgery were reported.(9,10) On obduction, the adrenal glands were atrophied, and their death was attributed to adrenal insufficiency after discontinuation of steroids before surgery without supplementation.

To prevent these complications in surgical patients considered to be at risk of steroid-induced (tertiary) adrenal insufficiency, it has been recommended to administer supplemental doses ("stress-dose") of steroids mimicking the normal cortisol response to stress around surgery.(9,10) However, the evidence supporting the use of a stress-dose of corticosteroids in patients at risk of tertiary adrenal insufficiency is of low quality, and some studies showed no benefit at all.(5,11–13) Therefore, important uncertainties remain whether such a stress-dose is necessary, and adherence to guidelines recommending a stress-dose consequently is low.(14,15) We aimed to investigate the effect of perioperative administration of a stress-dose of corticosteroids on patients' wellbeing and recovery after surgery in patients at risk of tertiary adrenal insufficiency.

METHODS

Study design and population

This retrospective single-center cohort study included patients who underwent elective non-cardiac surgery under general or regional anesthesia at the University Medical Center in Utrecht between January 2017 and June 2018, and who were at risk for developing tertiary adrenal

insufficiency. According to our local protocol that is based on a national guideline, patients are considered at risk of tertiary adrenal insufficiency if using an equivalent of 7.5 milligrams or more of oral prednisone for more than two weeks.(16) Patients with primary or secondary adrenal insufficiency, undergoing any type of pituitary gland surgery, undergoing emergency surgery, undergoing minor procedures under local anesthesia or sedation, or who were already admitted to the intensive care unit before surgery were excluded. Ethical approval for this study (19/673) was provided by the Ethical Committee UMC Utrecht Medical Research Ethics Committee, Utrecht, the Netherlands, under supervision from Prof. dr. L. Bont on October 8, 2019. Reporting was according to the STROBE guidelines.

Corticosteroid stress-dose protocol

According to the local protocol and national guideline, the recommended stress-dose depends on the magnitude of the surgical procedure.(16–18) In patients undergoing low-risk surgery (risk classification according to the 2014 ESC/ESA guidelines, the recommended stress-dose is 50 mg hydrocortisone (or equivalent) intravenously or intramuscularly during induction of anesthesia, in addition to their own daily steroid dosage. In case of hemodynamic instability, the hydrocortisone bolus is increased to 100 mg. In patients undergoing intermediate or high-risk surgery, a continuous intravenous hydrocortisone infusion of 150-200 mg/24 hours is recommended, plus a bolus of 25 mg (intermediate risk surgery) or 50 mg (high risk surgery) hydrocortisone at induction of anesthesia (Appendix 1). In this study all administered corticosteroid dosages were recorded and were converted to an equivalent hydrocortisone dosage (Appendix 2).(16,19,20)

Outcome

The primary outcome was the occurrence of any symptom of adrenal insufficiency during the first three in-hospital postoperative days: fatigue or feeling weak, nausea, vomiting, loss of appetite, muscle- and joint-aches. Duration of hospital stay was investigated as a secondary outcome.

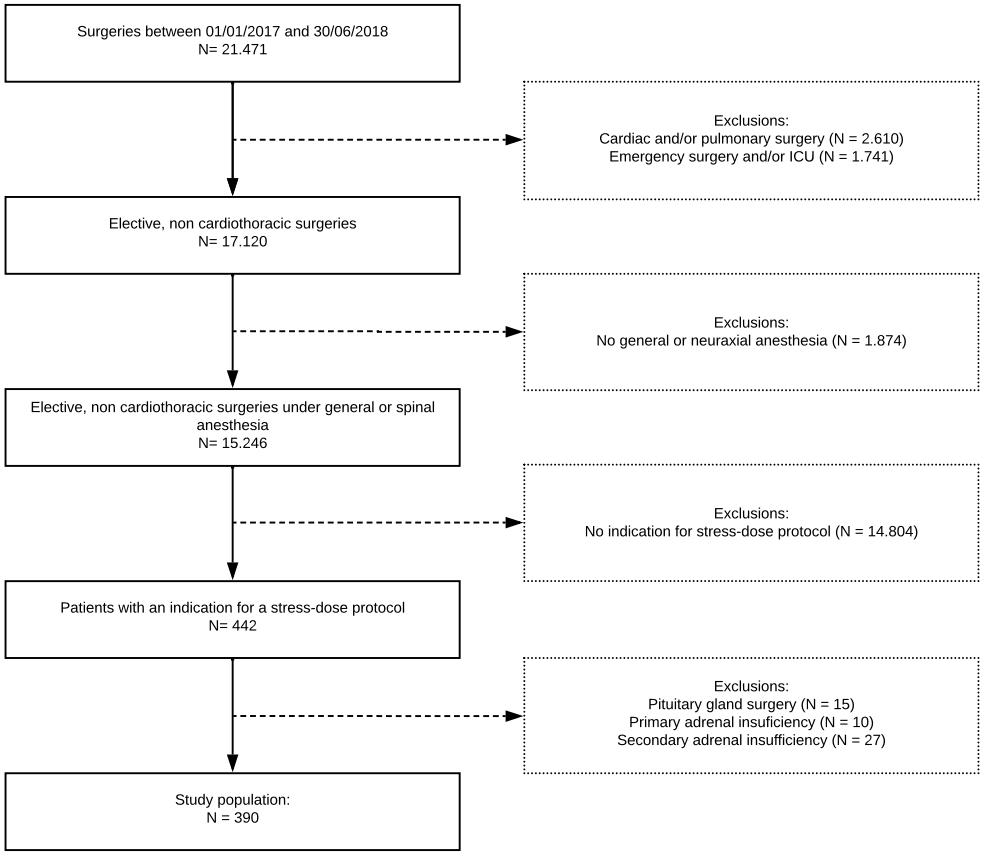
Data collection

Data were obtained from the hospital's electronic record keeping system (HiX, Chipsoft, The Netherlands), including patient characteristics and comorbidities, administration of perioperative corticosteroids, and the daily medical notes.

Statistical analysis

Patients were divided into three groups based on whether they received a stress-dose according to protocol: (1) stress-dose corticosteroid administered according to protocol (equivalent dose), (2) additional corticosteroid administered, but the dose was not equivalent to the recommended stress-dose (non-equivalent dose), (3) no corticosteroid administered in addition to their chronic daily dose.

Figure 1. Flowchart



Abbreviations: ICU, intensive care unit; N, number

Categorical data were described as absolute numbers (N) and frequencies (%). Continuous data were described using means and standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate.

The primary outcome was compared between the three groups using logistic regression analysis, with adjustment for confounding using

inverse probability treatment weighing (IPTW). First, ordinal regression analysis was performed to determine IPTW, in which the group that did not receive additional corticosteroids (group 3) was the reference group. Variables in this model were selected based on clinical experience and availability. All data used for the IPTW were complete. The standardized mean difference (SMD) was used to assess covariate balance between groups following propensity score matching, based on all included variables (Appendix 3). Next, the IPTW was used in a logistic regression analysis for the occurrence of the outcome.

Finally, subgroup analyses using chi-square testing were performed for the primary outcome in two subgroups: 1) Patients undergoing intermediate to high-risk surgical procedures, because patients undergoing low risk procedures were often discharged on the day of surgery; and 2) patients undergoing non-neurosurgical procedures, because patients undergoing neurosurgical procedures often received dexamethasone as prescribed by the neurosurgeon.

Data were analyzed using RStudio Team (2020, RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/). Both the "MASS" package (version 7.3.60.2) and the "dply" package (version 1.1.4) were used for the IPTW.

RESULTS

Of the 21,471 adult patients undergoing surgery during the study period, 390 patients (2%) were at risk of a tertiary adrenal insufficiency and were included (Figure 1). Approximately half of the patients were female (46%), the median age was 56 (IQR 45-69), and 220 patients (56%) had ASA class 3 or higher. Of the 390 patients, 94 patients (24%) received a corticosteroid stress-dose according to protocol, 125 patients (32%) received non-equivalent additional dosages, and 171 patients (44%) receive- page 7- page 7d no additional corticosteroids (Table 1). The surgical risk according to the ESC/ESA guidelines, surgical specialty and the surgery duration were statistically significantly different between the three groups (p-value <0.001).(19,21)

Table 1. Baseline characteristics

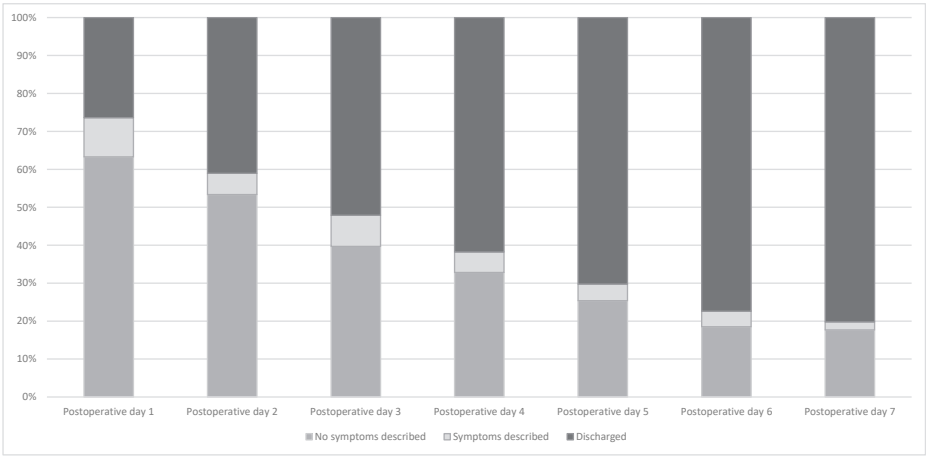
		Corticosteroid stress-dose		
		Equivalent N = 94	**Non-equivalent** N = 125	**None** N = 171
Age, median (IQR)		53 (45-67)	61 (45-69)	56 (44-70)
Female, N (%)		41 (44)	56 (45)	81 (47)
BMI in kg/m^2, median (IQR)		26 (23-29)	25 (23-28)	25 (22-30)
Pulmonary disease, N (%)		16 (17)	18 (14)	16 (9)
Diabetes, N (%)	IDDM	9 (10)	19 (15)	26 (15)
	NIDDM	11 (12)	9 (7)	21 (12)
Surgical risk*, N (%)	Intermediate/high	33 (35)	123 (98)	88 (52)
ASA classification, N (%)	3 and 4	49 (52)	63 (50)	107 (63)
Surgical specialty, N (%)	General	15 (16)	26 (21)	33 (19)
	Head and neck	33 (35)	6 (5)	38 (22)
	Neurosurgery	12 (13)	60 (48)	35 (21)
	Orthopedic	7 (7)	9 (7)	16 (9)
	Urogenital	14 (15)	9 (7)	25 (15)
	Vascular	9 (10)	14 (11)	16 (9)
	Other	4 (4)	1 (1)	8 (5)
Surgery duration^, median (IQR)		89 (51-166)	142 (96-223)	88 (62-147)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IDDM, insulin dependent diabetes mellitus, IQR, interquartile range; N, number; NIDDM, non-insulin dependent diabetes mellitus

* according to ESC guideline

In 186 patients (48%) data on the primary outcome were complete for the first three postoperative days. The remaining 204 patients (52%) had been discharged by the third postoperative day, of whom 106 patients already had been discharged after the first postoperative day (Figure 2). In the entire study population, 92 patients (24%) had any symptom during the first three postoperative days. Most symptoms were present in patients who received a non-equivalent corticosteroid dose (36 patients [39%]). Nausea and fatigue were noted most frequently, in 52 patients (13%) and 34 patients (9%), respectively (Table 2).

Figure 2. Postoperative symptoms



All patients were included in the IPTW analysis. The results of the maximum standardized mean differences before and after weighting are shown in Appendix 3. However, due to constraints in the number of available variables, no changes were made to the propensity score based on the balance. When compared with not administering a stress dose, neither the treatment with an equivalent stress-dose, nor with a non-equivalent dose was associated with the presence of postoperative symptoms in the first three postoperative days, (OR 1.5, 95% CI 0.5-4.0 and OR 1.4, 95% CI 0.5-3.5, respectively).

Subgroup analysis

Two subgroup analyses were performed. In the subgroup of patients who underwent intermediate to high-risk procedures (N=203) the primary outcome occurred in 18% in the equivalent doses group, in 51% in the non-equivalent doses group, and in 31% in the no corticosteroids group. There was no difference in postoperative length of stay (Appendix 4).

In the subgroup of patients who underwent non-neurosurgical procedures (N=195), the primary outcome occurred in 28% in the equivalent dose group, in 36% in the non-equivalent group, and in 36% in the no stress dose group (p-value=0.08). In the crude analysis of length of stay, patients treated with non-equivalent doses stayed longer in the hospital (median 4 days [IQR 2-10]), compared to patients with equivalent dosages (median 2 [IQR 1-4]) and those who received no stress dose (median 1 day [IQR 0-5], p-value < 0.01) (Appendix 4).

Table 2. Postoperative symptoms in first three postoperative days

		Corticosteroid stress-dose		
		Equivalent N = 94	**Non-equivalent** N = 125	**None** N = 171
Any symptoms, N (%)		24 (26)	36 (39)	32 (35)
Specified symptoms, N (%)	Fatigue or feeling weak	12 (13)	18 (14)	15 (9)
	Nausea and/or vomiting	13 (14)	23 (18)	16 (9)
	Loss of appetite	5 (5)	5 (4)	12 (7)
	Joint or muscle aches	0 (0)	0 (0)	0 (0)
Hospital admission in days, median (IQR)		2 (1-4)	4 (2-5)	2 (1-5)

IQR, interquartile range

DISCUSSION

This study including non-cardiac surgery patients at risk for tertiary adrenal insufficiency investigated the effect of a stress-dose of corticosteroids on the occurrence of postoperative symptoms of such insufficiency (e.g., nausea and vomiting, muscle aches, low appetite and fatigue). The presence of symptoms in the first three postoperative days was comparable between groups of patients who received a dose according to the guidelines, a non-equivalent dose (i.e. lower than recommended) or no stress-dose at all.

To our knowledge, this one of the first studies investigating symptoms of tertiary adrenal insufficiency after surgery in patients who are considered at risk for such symptoms and who did not did not receive perioperative supplemental corticosteroids. We used data from this cohort to follow-up on our previously published study about reasons for non-adherence to a stress-dose protocol. Although the data are somewhat older, the current protocol has not changed since then. Obviously, this study has some important limitations. First, due to its retrospective design, the occurrence of adverse symptoms may be underreported, and because 27% of patients were discharged on the first postoperative day, symptoms occurring after discharge were missed. Second, approximately a third of patients underwent neurosurgery. As patients undergoing intracranial procedures may require a specific corticosteroid regimen as determined by the neurosurgeon, this may have influenced the presence of symptoms investigated in this study. However, a subgroup analysis excluding all neurosurgery patients showed no difference in the presence of symptoms

or hospital stay. Moreover, we applied IPTW to adjust for baseline differences between the groups. After this adjustment, no significant difference was found. The type of anesthetic was not adjusted for in the analysis. As volatile anesthetics increase the risk of symptoms that may be associated with adrenal gland insufficiency (i.e. nausea and vomiting), this may have influenced the results. (22) Third, although the sample size was not sufficient to draw definitive conclusions, the differences in incidence of symptoms within a subgroup of 203 patients undergoing intermediate to high-risk surgery are considerable (18% in the group that received an equivalent dose, 51% in the group that received a non-equivalent dose, and 31% in the group that received no corticosteroids at all), which calls for a better understanding of these differences. Almost half of the patients received another corticosteroid than recommended in the protocol (i.e. hydrocortisone). Dexamethasone was often used for the prevention of postoperative nausea and vomiting, or as part of multimodal pain management.(23) Even though these prescriptions of corticosteroids are not according to the protocol, it may have been considered as an adequate dose in the prevention of tertiary adrenal insufficiency by the anesthesiologist, as other corticosteroids may also be administered as a stress-dose instead of hydrocortisone.(24)

The recommendation for the administration of corticosteroid stress-doses around surgery is built upon evidence of low quality. Nevertheless, these recommendations have been in place for over seventy years. A systematic review that was published in 2018 found no increased risk of perioperative hemodynamic instability when comparing placebo to corticosteroids in patients chronically using corticosteroids.(25) This systematic review included small studies, with a total of 37 patients in two randomized clinical trials and 462 patients in five cohort studies. No significant difference in the outcome of hemodynamic instability was reported, but the quality of the evidence was considered low. No new cohorts or RCTs have since been published, particularly none studying postoperative recovery.

Based on the present study and previous studies, there is not enough evidence to suggest that postoperative patients at risk of tertiary adrenal gland insufficiency have an impaired quality of recovery. Given the limitations of these studies however, it remains unclear if a corticosteroid stress-dose improves the quality of recovery and decreases the incidence of postoperative symptoms associated with a tertiary adrenal insufficiency after non-cardiac surgery. We believe that ultimately

an RCT is warranted to eliminate indication bias and to elucidate the necessity for perioperative corticosteroids.

CONCLUSION

This study in patients chronically using corticosteroids and undergoing non-cardiac surgery showed no difference in postoperative symptoms that may be associated with tertiary adrenal insufficiency between patients who received a stress-dose corticosteroids according to protocol and those not receiving it. Due to its retrospective design however, symptoms may have been underreported. More evidence of good quality is needed to fully answer this conundrum. However, we future research investigating this subject, should focus on the more subjective outcome (e.g. postoperative symptoms) rather than hemodynamic instability.

REFERENCES

1. Kinnett K, Noritz G. [MD-17-0009] The PJ Nicholoff Steroid Protocol for Duchenne and Becker Muscular Dystrophy and Adrenal Suppression. PLoS Curr. 2017;
2. Lamberts S, Bruining H, de Jong F. Corticosteroid Therapy in Severe Ilness. New England Journal of Medicine. 1997;337(18):1285–92.
3. Yong SL, Coulthard P, Wrzosek A. Supplemental perioperative steroids for surgical patients with adrenal insufficiency. Cochrane Database of Systematic Reviews. 2013;2013(10).
4. Salem M, Tainsh RE, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage: A reassessment 42 years after emergence of a problem. Annals of Surgery. 1994.
5. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – A systematic review. Dan Med J. 2018;65(6):1–5.
6. Seo KH. Perioperative glucocorticoid management based on current evidence. Anesth Pain Med (Seoul). 2021;16(1):8–15.
7. Lehmann M, Monte K, Barach P, Kindler CH. Postoperative patient complaints: a prospective interview study of 12,276 patients. J Clin Anesth. 2010;22(1):13–21.
8. T. Woodcock, P. Barker, S. Daniel, S. Fletcher, J. A. H. Wass, J. W. Tomlinson, U. Misra, M. Dattani, W. Arlt AV. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency. Anaesthesia. 2020;
9. Fraser CG, Preuss FS, Bigford WD. Adrenal atrophy and irreversible shock associated with cortisone therapy. J Am Med Assoc. 1952;
10. Leon Lewis, Robert F Robinson, James Yee, Lucy A Hacker GE. Fatal adrenal cortical insufficiency precipitated by surgery during prolonged continuous cortisone treatment. Ann Intern Med. 1953;39(1):116–26.
11. Freudzon L. Perioperative steroid therapy: Where's the evidence? Curr Opin Anaesthesiol. 2018;31(1):39–42.
12. Glowniak J V., Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery. 1997;121(2):123–9.
13. de Lange DW, Kars M. Perioperative glucocorticosteroid supplementation is not supported by evidence. Eur J Intern Med. 2008;19(6):461–7.
14. Barker OJH, Ramesh A V., Kangesan I, Barnes J, Harrogate S, Gupta S, et al. Peri-operative Replacement of Exogenous Steroids (PREdS): a national audit of current peri-operative prescribing for patients taking therapeutic steroids. Anaesthesia. 2024 Oct 3;79(10):1042–52.
15. Miggelbrink LA, Marsman M, van de Wetering J, van Klei WA, Kappen TH. Peri-operative corticosteroid supplementation guideline adherence. Anaesthesia. 2025 Jan 30;
16. BijnierNET. Kwaliteitsstandaard Bijnieraandoeningen. 2017;Version 3.
17. Coursin DB, Wood KE. Corticosteroid Supplementation for Adrenal Insufficiency. 2013;287(2):236–40.
18. Chilkoti G, Singh A, Mohta M, Saxena A. Perioperative "stress dose" of corticosteroid: Pharmacological and clinical perspective. Journal of Anaesthesiology Clinical Pharmacology. 2019.

19. Lamperti M, Romero CS, Guarracino F, Cammarota G, Vetrugno L, Tufegdzic B, et al. Preoperative assessment of adults undergoing elective noncardiac surgery: Updated guidelines from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol. 2025 Jan 1;42(1):1–35.
20. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur Heart J. 2014;35(35):2383–431.
21. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022 Oct 14;43(39):3826–924.
22. Schraag S, Pradelli L, Alsaleh AJO, Bellone M, Ghetti G, Chung TL, et al. Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: a systematic review and meta-analysis. BMC Anesthesiol. 2018 Nov 8;18(1):162.
23. Henzi I, Walder B, Tramer M. Dexamethasone for the prevention of postoperative nausea and vomiting: A quantitative systematic review. Anesth Analg. 2000;90:186–94.
24. Oprea A, Bonnet NCG, Pollé O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther Adv Endocrinol Metab. 2019;10:2042018818821294.
25. Groleau C, Morin SN, Vautour L, Amar-Zifkin A, Bessissow A. Perioperative corticosteroid administration: a systematic review and descriptive analysis. Perioperative Medicine. 2018;7:1–8.

SUPPLEMENTARY FILES

S1. Perioperative corticosteroid stress dose protocol

Surgical risk	Day of surgery	Postoperative day 1	Postoperative day 2	Postoperative day 3	Postoperative day 4 through 6
Low*	50mg hydrocortisone i.v. or i.m.	Double dose of regular corticosteroid	Double dose of regular corticosteroid	Resume regular dose	N.A.
Intermediate*	150mg/24h hydrocortisone pump + 25mg bolus i.v.	40-20-20mg hydrocortisone orally or i.v.	20-20-20mg hydrocortisone orally or i.v.	20-10-10mg hydrocortisone orally	**Day 4**: Resume regular dose
High*	200mg/24h hydrocortisone pump + 50mg bolus i.v.	100mg/24h hydrocortisone pump i.v.	40-20-20mg hydrocortisone orally or i.v.	20-20-20mg hydrocortisone orally	**Day 4**: 20-10-10mg hydrocortisone orally
					Day 5: 15-10-15mg hydrocortisone orally
					Day 6: resume regular dose

All dosage recommendations are based on the local perioperative protocol which is based on the national guideline.

*100mg hydrocortisone i.v. in case of hemodynamic instability at any moment during the perioperative period

h, hours; i.m., Intra-muscularly; i.v., intravenously; mg, milligrams; N.A., not applicable

S2. Conversion table of equivalent corticosteroid dosages.

Corticosteroid	Equivalent dose (mg)
Hydrocortisone	20
Cortisone	25
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Betamethasone	0.75
Dexamethasone	0.75

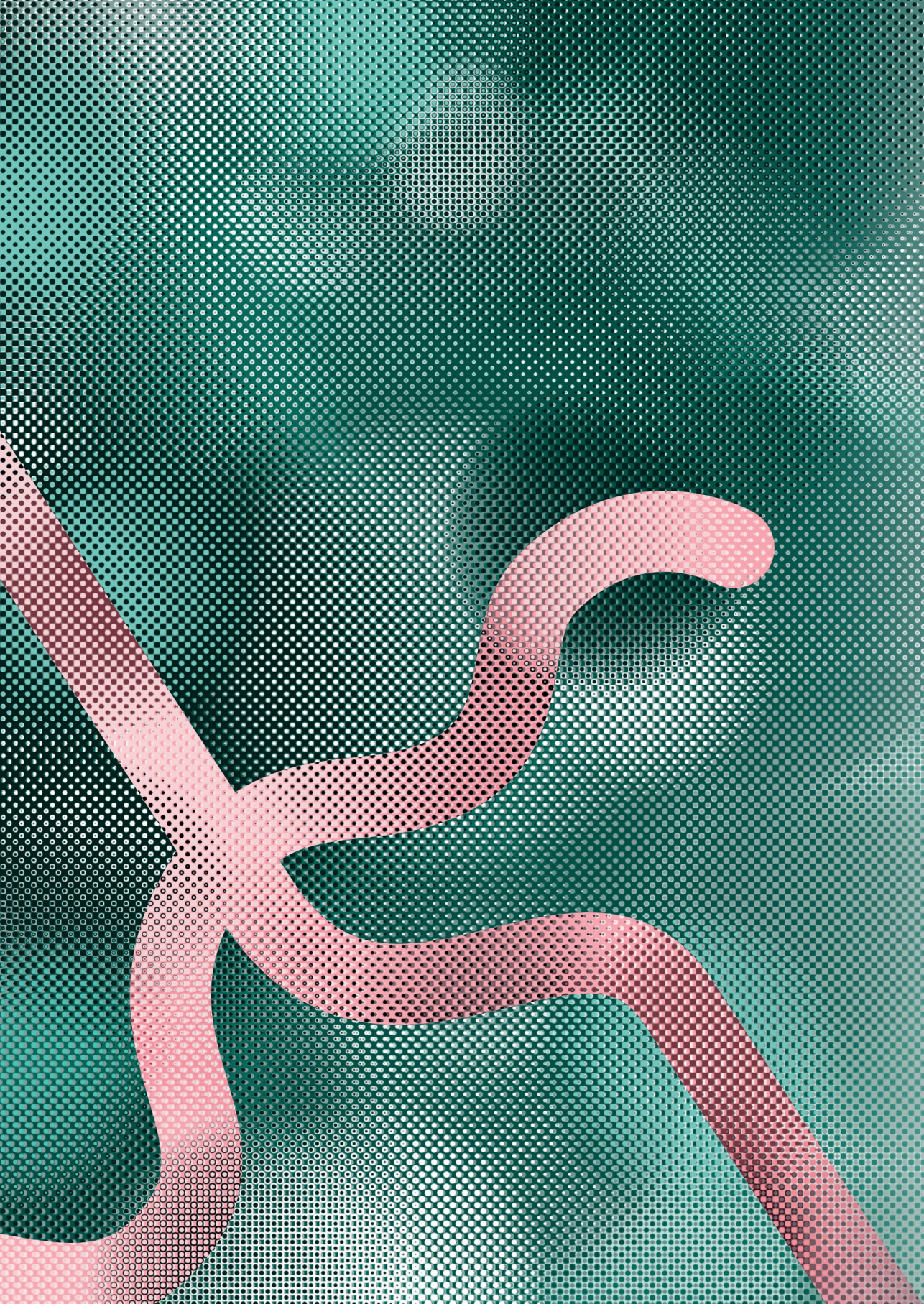
Abbreviations: mg, milligrams

S3. Balancing of variables for propensity score

Variable		Unadjusted Maximum Standardized mean difference	Adjusted Maximum Standardized mean difference
Age		0.20	0.17
Gender		0.034	0.017
Pulmonary disease		0.076	0.0092
Diabetes	*No*	0.064	0.017
	NIDDM	0.057	0.045
	IDDM	0.052	0.061
ASA	*1*	0.043	0.037
	2	0.13	0.022
	3	0.14	0.061
	4	0.029	0.026
BMI		0.12	0.099
Duration		0.78	0.47
Cardiac risk	Intermediate/high	0.63	0.63
Specialty	General	0.045	0.065
	Head	0.30	0.27
	Neurosurgery	0.35	0.34
	Orthopedic	0.022	0.012
	Urogyn	0.077	0.10
	Vascular	0.018	0.018
	Other	0.039	0.062
Interaction term	specialty*duration	Not shown	Not shown

S4. Subgroup analysis

	Equivalent stress dose	Non-equivalent stress dose	No corticosteroids	P-value
	Intermediate to high-risk procedures			
	N = 31	N = 102	N = 70	
Any symptoms during first three postoperative days, N (%)	12 (18)	35 (51)	21 (31)	0.7
Hospital length of stay in days, median (IQR)	6 (4-8)	4 (2-7)	4 (2-7)	0.1
	Non-neurosurgical procedures			
	N = 60	N = 52	N = 83	
Any symptoms during first three postoperative days, N (%)	19 (28)	25 (36)	25 (36)	0.08
Hospital length of stay in days, median (IQR)	2 (1-4)	4 (2-10)	1 (0-5)	< 0.005



CHAPTER 7

Efficacy of perioperative glucocorticoid suppletion in surgical patients at risk of tertiary adrenal gland insufficiency on quality of recovery, an observational cohort study.

L.A. Miggelbrink (1), T.H. Kappen (1), R.W.H. van Oorschot (1), C.E. de Keyser (2), W.A. van Klei (1,3,4,5), J.A.R. van Waes (1)

Department of 1. Anesthesiology, 2. Endocrinology from the University Medical Centre Utrecht, Utrecht University, the Netherlands

Department of 3. Anesthesiology and Pain Management, Toronto General Hospital, University Health Network Toronto, Toronto Ontario, Canada

Department of 4. Anesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Department of 5. Anesthesiology and Pain Management, Toronto General Hospital Research Institute, Toronto, Ontario, Canada

Under review

ABSTRACT

Introduction: Patients who chronically use glucocorticoids are at risk for tertiary adrenal gland insufficiency (AI). Guidelines advise stress dosages of glucocorticoids around surgery in these patients. Evidence supporting this strategy is limited and guideline adherence low. We therefore aimed to study the effect of a perioperative glucocorticoid stress-dose on quality of recovery in these patients.

Methods: This prospective observational study included patients at risk for tertiary AI and control patients undergoing elective non-cardiac surgery. Three groups were compared: 1) patients at risk of AI who did not receive a stress-dose, 2) patients at risk of AI who did receive a stress-dose, 3) control patients not at risk of AI. The primary outcome Quality of Recovery (QoR-15) on the first seven postoperative days was compared between these groups using mixed-effects regression analysis resulting in partial-effect plots. Inverse probability weighting was used to adjust for confounding.

Results: In total 54 patients at risk for AI were included, of whom 37 patients (69%) received a stress-dose and 17 (31%) received no stress-dose, and 52 control patients. Crude analysis showed a mean (±SD) QoR-15 score on postoperative day 1 of 86 (±22), 99 (±19), and 95 (±24), in group 1, 2 and 3 respectively (p-value 0.26). The adjusted analysis showed a significantly impaired recovery on the first two postoperative days in patients at risk of AI who did not receive a stress-dose.

Conclusion: In this small-sized observational study, we observed a lower QoR-15 score in surgical patients at risk for AI who did not receive a glucocorticoid stress-dose. This impaired recovery may have continued throughout the first week, but the small sample size did not allow for definitive conclusions. An adequately powered randomized study is needed to confirm these findings.

Key words: quality of recovery, tertiary adrenal gland insufficiency, steroid induced adrenal gland insufficiency, glucocorticoids, perioperative, surgery

INTRODUCTION

Cortisol is the main glucocorticoid and plays a vital role in regulating various bodily functions, including metabolism, inflammation, blood pressure, and the sleep-wake cycle. It is produced by the adrenal gland and regulated by the hypothalamic-pituitary-adrenal (HPA) axis.(1) Stress on the body, including surgery, increases cortisol levels to cope with increased cortisol requirement.(2) The more invasive a surgical procedure is, the higher are the levels of produced cortisol.(3)

However, chronic glucocorticoids usage for various indications including autoimmune, inflammatory and pulmonary diseases, may suppress the hypothalamic-pituitary-adrenal axis leading to a tertiary adrenal gland insufficiency (AI). As an increasing number of patients is taking glucocorticoids chronically, currently 2.5% of the population, this is an important issue to address in the perioperative care of surgical patients.(4) In case of surgical stress, a lack of cortisol may lead to mild atypical symptoms (e.g. fatigue, muscles aches, loss of appetite, nausea and vomiting) or more severely, to hemodynamic instability.(5,6) Based on some old case reports showing atrophied adrenal glands in patients who died unexpectedly during surgery, it is recommended to administer a supraphysiological dose of glucocorticoids (stress-dose) around surgery in patients chronically using glucocorticoids in order to prevent AI.(1) The evidence supporting this recommendation, however, is of low quality, and some studies showed no benefit at all.(7–9) In a recent retrospective cohort study we also found no difference in postoperative symptoms between patients who received a stress-dose of glucocorticoids and those not receiving it.(10) Because of this lack of evidence, we aimed to prospectively investigate the effect of perioperative supraphysiological glucocorticoid administration on quality of recovery in surgical patients chronically using glucocorticoids.

METHODS

We conducted a prospective, observational cohort study between September 2022 and September 2023 at the University Medical Center Utrecht, The Netherlands. Eligible patients were those undergoing a non-cardiac surgical procedure under (loco)regional or general anesthesia, and using prednisone ≥7,5mg (or equivalent dose of another glucocorticoid, appendix 1) for ≥3 weeks, i.e. those considered to be at risk for tertiary AI

around surgery. Exclusion criteria were (suspected) primary or secondary AI, surgical procedures to the pituitary gland, and the inability to fill out questionnaires (e.g. language barrier or cognitive impairment). Patients with intracranial tumor s presenting for neurosurgery initially were included in the study. However, as glucocorticoids were often prescribed by the neurosurgeon before and after surgery for treatment of cerebral edema which interfered with the glucocorticoid stress-dose protocol, the study protocol was amended to exclude neurosurgical patients. After each included patient at risk of tertiary AI, one control patient was included. Consecutive patients undergoing a similar surgical procedure but not using glucocorticoids were eligible as control patients.

The study protocol was presented and approved by the Medical Ethics Committee (METC NedMec, 22/733).

Glucocorticoid stress-dose protocol

During the study period, a local protocol based on a national guideline was in use describing indications for glucocorticoid stress-dose administration and the recommended dosages around surgery (appendix 2). The perioperative dosage of glucocorticoids depended on the surgical risk, which was based on the guideline for non-cardiac surgery by the European Society of Cardiology and European Society of Anesthesiology and Intensive Care.(11)

Outcome

The primary outcome was the validated Quality of Recovery-15 (QoR-15) score on the first seven postoperative days. Secondary outcomes included the QoR-15 score plus 5 additional questions addressing symptoms that specifically may occur in patients with AI, each specific item of the QoR-15 questionnaire and 5 additional questions, hemodynamic instability defined as refractory hypotension despite adequate treatment, in-hospital complications (e.g. infection, arrhythmias, unexpected intensive care admission), and postoperative length of stay.

Study procedures and data collection

After informed consent was obtained, patients received postoperative questionnaires every day for the first 7 postoperative days, either on paper or electronically by email. This questionnaire contained 15 questions from the QoR-15 questionnaire and the 5 additional questions (appendix 3). Patients who wished to receive electronic questionnaires also received daily reminders to fill out the questionnaires by email. Patients who

had received questionnaires on paper were contacted by telephone as a reminder to complete and return the forms.

Data regarding patient (e.g. characteristics and comorbidities) and surgical specific information (e.g. type of surgery, type of anesthesia, duration of surgery) were obtained from the hospital's electronic record keeping system (HiX, Chipsoft, the Netherlands).

Statistical analysis

Patients were divided into three groups depending on glucocorticoid administration: (1) patients at risk for AI, but glucocorticoids were not administered according to the stress-dose protocol, i.e. glucocorticoids may have been administered but the dose was lower than the recommended stress-dose, or no glucocorticoid was administered at all, (2) patients at risk for AI, and a glucocorticoid stress-dose was administered according to the stress-dose protocol, (3) control patients not at risk for AI. To determine whether the administered glucocorticoid dose was equivalent to the recommended dose according to the stress-dose protocol, this was converted into hydrocortisone dosages (appendices 1 and 2). If glucocorticoid dosages were less than the recommended dose, patients were classified into the 'no stress-dose' group (group 1), and if glucocorticoid dosages were equal or more than the total recommended dose, patients were classified into the 'stress-dose' group (group 2).

Participants who did not complete the questionnaires on a day-by-day basis were considered lost to follow-up and excluded from the analysis. However, if they had completed part of the week-long questionnaire beginning on postoperative day 1, their data were included for the specific days they had completed.

Categorical data were described using absolute numbers (N) and frequencies (%) and compared between groups using ANOVA, the Chi-Square test or Fisher's exact test where appropriate. Continuous data was described using mean and standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. A p-value of <0.05 was considered as statistically significant.

The primary outcome quality of recovery on each postoperative day was compared using ANOVA. Next, the primary longitudinal outcome was compared between patients at risk of AI receiving a stress-dose and patients at risk of AI not receiving this using a mixed-effects

regression model with adjustment for possible confounding using inverse probability weighting (IPTW). This allowed us to account for baseline differences, as well as the varying recovery over time across groups. First, logistic regression analysis was performed to calculate IPTW estimates. Variables in this model were based on clinical experience and availability, and included age, sex, American Society of Anesthesiologist (ASA) classification, diabetes mellitus, duration of surgery, surgical risk, surgical specialty, the use of total intravenous anesthesia, and the indication for chronic use of glucocorticoids. Next, the IPTW was used in a mixed-effects regression model in which time (e.g. postoperative days 1 through 7) was used as a timepoint. As the relation between time and the quality of recovery was non-linear, splines with three knots were incorporated into the regression model for both the fixed effects (administration of a stress-dose, and time) as well as the random effects by participants (random slope, random intercept). Model estimation was performed using maximum likelihood. Predictions from the fitted model were used to predict the expected outcome. Both the standard errors (SE) of the predictions and the 95% confidence intervals (95% CI) of the predictions were used to quantify uncertainty.

To interpret the estimates and uncertainty of the mixed-effects regression model, partial effect plots were constructed, displaying the predicted trajectories of recovery over time for each treatment group. This allowed the visualization of the estimated nonlinear effects to compare the groups. After that, this analysis for the primary outcome was repeated including only control patients, to check whether glucocorticoid administration (e.g. as prophylaxis or treatment of postoperative nausea and vomiting) influenced quality of recovery in patients who were not at risk of AI. Statistical significance was reached if the confidence interval of the partial effect plot of one group did not intercede with the predicted quality of recovery of the other group.

Finally, secondary outcomes were compared using ANOVA for continuous variables and the chi-square test for dichotomous variables.

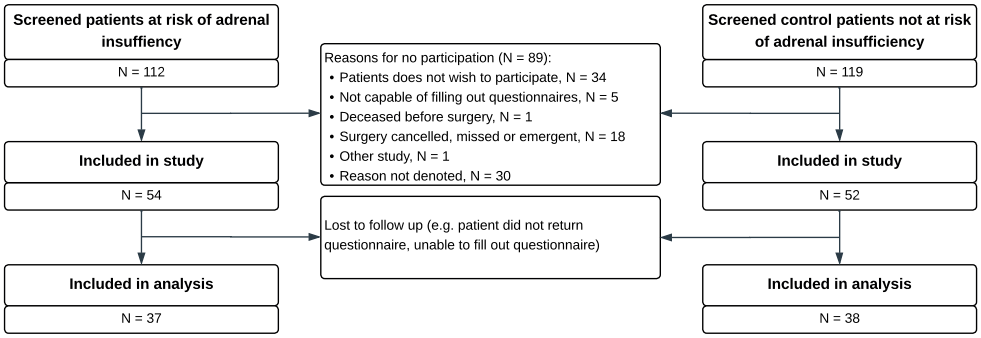
Data was analyzed using Rstudio Team (2020, Rstudio: Integrated Development for R. Rstudio, PBC, Boston, MA, URL http://www.rstudio.com/). Both the "MASS" package (version 7.3.60.2) and the "dply" package (version 1.1.4) were used for the IPTW. Both the "nlme" package (version 3.1.168) and the "rms" package (version 6.8.2) were used for

the mixed-effects regression model with splines. The "ggplot2" package (version 3.5.1) was used for the partial effect plot.

RESULTS

During the recruitment period 112 surgical patients at risk for AI were eligible for inclusion, of whom 54 patients were included in the study. A total of 119 patients were deemed eligible as control patients, of whom 52 patients were included in the study (Figure 1). Of the included patients, 17 patients at risk of AI and 14 control patients did not complete any of the postoperative questionnaires and were therefore excluded from the analysis.

Figure 1. Flowchart



Of all 106 included patients, 62 were male (58%) with a median age of 58 (IQR 49-68) years. Most patients had ASA classification of three or four (62 patients, 58%). The most common comorbidities were hypertension (46 patients, 43%), renal insufficiency (22 patients, 21%) and cancer (42 patients, 40%). Most patients received total intravenous anesthesia (96 patients, 91%). The most common indication for chronic usage of glucocorticoids was a history of transplant surgery (Table 1).

Table 1. Baseline characteristics

		No stress-dose dose N = 17	Stress-dose N = 37	Control group N = 52
Male gender, N (%)		8 (47)	21 (57)	33 (63)
Age in years, median (IQR)		56 (32-80)	57 (32-83)	59 (28-91)
BMI in kg/m^2, median (IQR)		25 (16-34)	25 (20-30)	27 (19-35)
ASA classification, N (%)	ASA 3/4	14 (82)	27 (73)	21 (40)
Medical history, N (%)	Hypertension	5 (29)	21 (57)	20 (38)
	Pulmonary disease	4 (24)	5 (14)	8 (15)
	Diabetes mellitus	3 (18)	11 (30)	5 (10)
	Renal insufficiency	5 (29)	13 (35)	4 (8)
	Cerebrovascular disease	2 (12)	1 (3)	3 (6)
	Cardiac disease	5 (29)	10 (	11
	Auto-immune disease	10 (59)	11 (30)	6 (12)
Surgical risk, N (%)	Low	4 (24)	19 (51)	15 (29)
	Intermediate	12 (71)	18 (49)	34 (65)
	High	1 (6)	0 (0)	3 (6)
Anesthesia type, N (%)	General	13 (76)	33 (89)	48 (92)
	General + locoregional	4 (24)	3 (8)	4 (8)
	Spinal block	0 (0)	1 (3)	0 (0)
TIVA, N (%)		16 (94)	31 (84)	49 (94)
Surgical characteristics	Intracranial, N (%)	0 (0)	3 (8)	5 (10)
	Oncologic, N (%)	5 (29)	7 (19)	20 (38)
	Duration, median (IQR)	140 (90-205)	113 (60-150)	115 (60-180)

Table 1. Continued

		No stress-dose dose N = 17	Stress-dose N = 37	Control group N = 52
Perioperative corticosteroid administration				
Indication stress dose, N (%)	Lung disease	0 (0)	1 (3)	NA
	Neurologic disorder	0 (0)	2 (5)	NA
	Renal disease	0 (0)	3 (8)	NA
	Rheumatology disease	7 (41)	2 (5)	NA
	Gastrointestinal disease	0 (0)	2 (5)	NA
	Other (e.g. transplant)	10 (59)	27 (73)	NA
Intraoperative, N (%)	Hydrocortisone	8 (47)	27 (73)	0 (0)
	Other	5 (29)	13 (35)	18 (35)
Postoperative day 1, N (%)	Hydrocortisone	10 (59)	27 (73)	0 (0)
	Other	8 (47)	9 (24)	4 (8)
Postoperative day 2, N (%)	Hydrocortisone	9 (53)	18 (49)	0 (0)
	Other	7 (41)	14 (38)	4 (8)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; N, number; TIVA, total intravenous anesthesia

When administered a stress-dose intraoperatively, most patients received hydrocortisone (27 patients, 73%). Intraoperative administration of hydrocortisone differed significantly between the three groups (47% vs 73% vs 0% in the no stress-dose group, stress-dose group, and control group, respectively, p-value<0.000), whilst the administration of other glucocorticoids did not (29% vs 35% vs 35%, p-value=0.91). Postoperative administration of both hydrocortisone and other glucocorticoids differed significantly between all three groups (Table 1).

Primary outcome

Crude analysis showed a mean QoR-15 score on postoperative day 1 of 86 (SD 22), 99 (SD 19), and 95 (SD 24), in the no stress-dose group (group 1), stress-dose group (group 2) and control group (group 3), respectively (p-value 0.26). Also, on the next postoperative days there was no crude difference in recovery (Table 2). However, the partial effect plots that resulted from the adjusted analysis showed a significant difference in QoR-15 in the patients who received a stress-dose as compared to patients who did not on postoperative days 1 and 2 (Figure 2a). No difference was observed between control patients with and without glucocorticoid administration around surgery (Figure 2b). The estimates from the mixed-effects model that were used in the partial effect plots are shown in Appendix 4.

Secondary outcomes

When five additional questions were added to the QoR-15, there was no difference in the crude quality of recovery between the three groups. Other secondary outcomes (in-hospital complications, hemodynamic instability, unexpected intensive care admission and admission duration), were also not different between groups (Table 2).

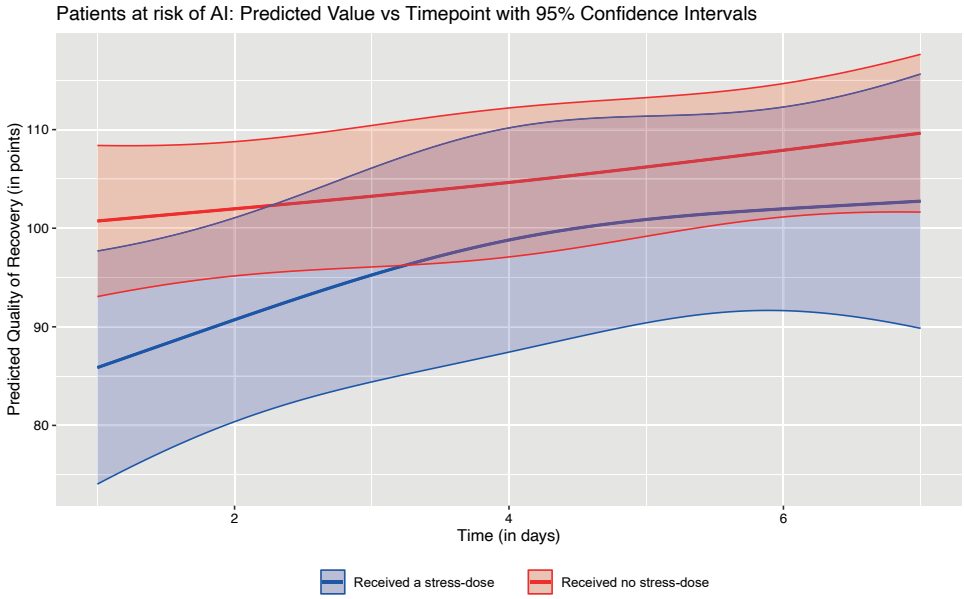
DISCUSSION

In this observational study we found that perioperative glucocorticoid supplementation according to a stress-dose protocol in surgical patients at risk of tertiary AI due to chronic glucocorticoid usage was associated with significantly better recovery on the first two postoperative days as compared to patients not receiving adequate glucocorticoid supplementation. No effect was observed on other outcomes, including in-hospital complications, hemodynamic instability, and intensive care admissions.

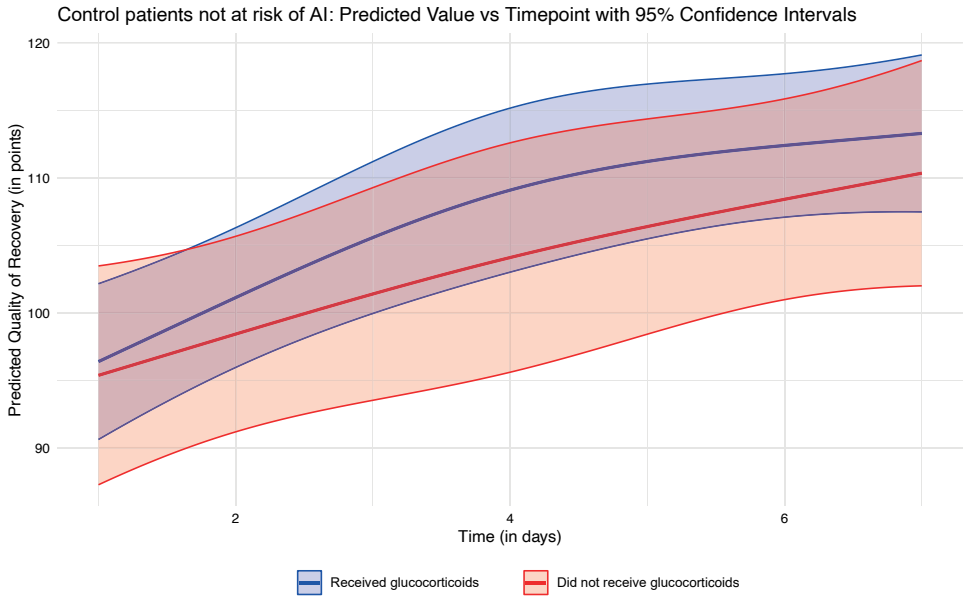
The findings of this study suggest that a perioperative glucocorticoid stress-dose may improve postoperative recovery on the first days after surgery in these patients, as a result of adequate s supplementation of a supposed glucocorticoid deficit. Some other studies described a beneficial effect of glucocorticoids on recovery in general surgical patients without AI.(12,13) This was not observed in the control group of our study, which may be explained by the small sample size of the control group.

Figure 2. Partial effect plots showing predicted QoR-15 scores over the first 7 postoperative days, with 95% confidence intervals. (2a) Patients at risk of tertiary adrenal insufficiency who received or did not receive a perioperative glucocorticoid stress-dose. (2b) Control patients who received or did not receive perioperative glucocorticoids.

2a. Partial effect plots for patients with an indication for a stress dose



2b. Partial effect plots for control patients



x-axis: Time (in days)

y-axis: Predicted QoR-15 score

The solid lines represent the predicted QoR-15 scores, and the shaded areas represent the 95% confidence intervals. The difference between groups in predicted QoR-15 score can be visually assessed at each time point. A difference between groups is suggested when the predicted value for one group and the 95% confidence interval for the other group do not overlap.

Table 2. Primary and secondary outcomes

	No stress-dose	Stress-dose	Control	P-value
Primary outcome: Quality of recovery				
Postoperative day 1	N = 12	N = 25	N = 38	
QoR-15*, mean ± SD	86 (±22)	99 (±19)	95 (±24)	P = 0.26
Plus 5 additional questions^, mean ± SD	124 (±25)	138 (±24)	132 (±33)	P = 0.38
Postoperative day 2	N = 12	N = 22	N = 38	
QoR-15*, mean ± SD	94 (±28)	102 (±18)	104 (±20)	P = 0.31
Plus 5 additional questions^, mean ± SD	132 (33)	139 (±25)	143 (±26)	P = 0.43
Postoperative day 3	N = 12	N = 22	N = 37	
QoR-15*, mean ± SD	97 (±28)	106 (±21)	106 (±23)	P = 0.43
Plus 5 additional questions^, mean ± SD	134 (±34)	143 (±28)	148 (±30)	P = 0.38
Postoperative day 4	N = 12	N = 22	N = 37	
QoR-15*, mean ± SD	99 (±22)	107 (±20)	110 (±23)	P = 0.33
Plus 5 additional questions^, mean ± SD	138 (±24)	145 (±27)	152 (±30)	P = 0.33
Postoperative day 5	N = 11	N = 23	N = 37	
QoR-15*, mean ± SD	104 (±20)	105 (±21)	112 (±23)	P = 0.42
Plus 5 additional questions^, mean ± SD	143 (±28)	142 (±29)	153 (±31)	P = 0.38
Postoperative day 6	N = 11	N = 21	N = 35	
QoR-15*, mean ± SD	105 (±17)	109 (±18)	117 (±20)	P = 0.15
Plus 5 additional questions^, mean ± SD	145 (±23)	146 (±26)	158 (±28)	P = 0.19
Postoperative day 7	N = 9	N = 21	N = 31	
QoR-15*, mean ± SD	106 (±22)	111 (±21)	121 (±19)	P = 0.08
Plus 5 additional questions^, mean ± SD	144 (±31)	150 (±27)	164 (±26)	P = 0.07

Table 2. Continued

	No stress-dose	Stress-dose	Control	P-value
Secondary outcomes	N = 17	N = 27	N = 52	
Duration admission, median (IQR)	5 (2-8)	3 (1-4)	3 (1-4)	P = 0.25
Hemodynamic instability, N (%)	0 (0)	0 (0)	0 (0)	P = 1.0
Complications, N (%)	6 (35)	8 (22)	11 (21)	P = 0.46
Unexpected ICU admission, N (%)	0 (0)	1 (3)	0 (0)	P = 0.39

* maximum score = 150

^ maximum score = 200

ICU, intensive care unit; N, number; QoR-15, quality of recovery questionnaire containing 15 questions; SD, standard deviation

As of today, it remains unclear which chronic dose and duration of glucocorticoid use warrants caution for the development of tertiary AI. Multiple studies looked at biochemical signs of AI after prolonged administration of (low dose) glucocorticoids. One meta-analysis investigating biochemical signs of AI in patients chronically using glucocorticoids found that 98 of 521 patients (19%) had biochemical results concurrent with AI. However, only 10% of these patients reported symptoms, whilst the other 90% did not.(14) Thus, it is not clear whether all patients with biochemically suppressed adrenal gland function are in need of a glucocorticoid stress-dose around surgery.

Current guidelines recommending stress-dosages are based on two small randomized clinical trials and some observational studies. The study published by Friedman et al, included 18 patients for various surgical procedures. One patient in the placebo group had hypotension which responded to adequate fluid resuscitation, and one patient in the intervention group developed hypotension due to excess opioids. None of the perioperative heart rate, blood pressure, or complications differed between the two groups.(15) The study performed by Thomason et al, investigated 20 patients with a previous organ transplant, undergoing surgery to remove gingival overgrowth. Each patient served as their own control, as the correction procedure consisted of 2 surgeries. No difference was found in blood pressures during the perioperative period.(16) Thus, with regard to perioperative hemodynamic shock, no convincing evidence exists to warrant supraphysiological dosages of glucocorticoids.(17)

We previously reported that this lack of evidence behind guidelines recommending a glucocorticoid stress-dose in patients at risk of AI was the main reason for non-adherence.(18) The compliance to these guidelines, both in our hospital as well as in the UK, is low (8-9%).(18,19) Anesthesiologists had little belief in the beneficial effects of glucocorticoid supplementation, at least when focusing on the prevention of hemodynamic instability, which is a rare phenomenon.(18)

Instead, we aimed to focus on more subtle symptoms of AI. This is the first study prospectively evaluating the quality of recovery in surgical patients at risk of tertiary AI, therefore addressing an important gap in evidence in perioperative care. The prospective observational design using a validated outcome measure (QoR-15) minimized the risk of patient recall bias, and allowed a day-by-day follow-up of postoperative recovery. The daily QoR-15 assessments allowed a detailed longitudinal

analysis, rather than relying on a single time-point, which increased the sensitivity for detecting differences between groups. Additionally, we attempted to increase the clinical relevance by including five tailored questions about specific symptoms of adrenal insufficiency.

This study has some obvious limitations. First, as this study was purely observational, residual confounding through indication bias may be present. We limited confounding as much as possible by performing a matched design to account for procedure type and anesthetic technique, and by using inverse probability weighting in a mixed-effects regression analysis to further adjust for possible confounders. Second, as there was a relatively high proportion of patients lost to follow-up which may have been the result of poor quality of recovery in specific groups, this may have led to attrition bias. However, loss to follow-up was comparable between the groups. Finally, the impaired recovery as found on the first two postoperative days may have continued throughout the first week, but the small sample size did not allow for definitive conclusions.

Future studies using designs to adequately deal with confounding are needed to confirm if a glucocorticoid stress-dose in patients at risk of tertiary AI indeed improves quality of recovery after surgery.

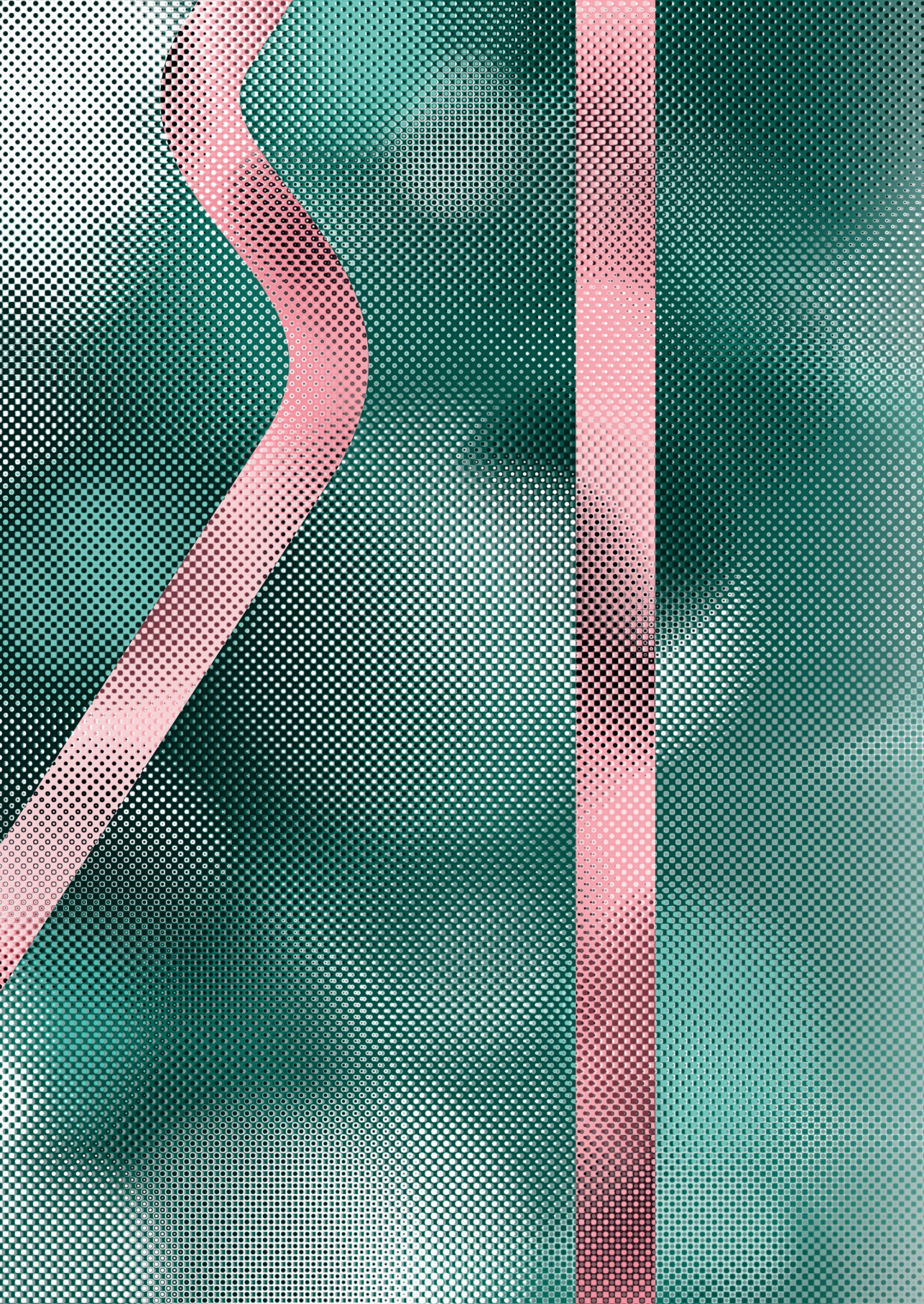
CONCLUSION

In this small-sized observational study, we observed a lower QoR-15 score in surgical patients at risk for AI who did not receive a glucocorticoid stress-dose. This impaired recovery may have continued throughout the first week, but the small sample size did not allow for definitive conclusions. An adequately powered randomized study is needed to confirm these findings.

REFERENCES

1. Seo KH. Perioperative glucocorticoid management based on current evidence. Anesth Pain Med (Seoul). 2021;16(1):8–15. doi:10.17085/apm.20089
2. Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, et al. The cortisol stress response induced by surgery: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018 Nov;89(5):554–67. doi:10.1111/cen.13820 PubMed PMID: 30047158.
3. Menger MM, Histing T, Laschke MW, Ehnert S, Viergutz T, Fontana J. Cortisol stress response after musculoskeletal surgery: a narrative review. EFORT Open Rev. 2025 Apr 1;10(4):186–92. doi:10.1530/EOR-2024-0126 PubMed PMID: 40167425.
4. Pazderska A, Pearce SH. Adrenal insufficiency - recognition and management. Clin Med (Lond). 2017 Jun;17(3):258–62. doi:10.7861/clinmedicine.17-3-258 PubMed PMID: 28572228.
5. T. Woodcock, P. Barker, S. Daniel, S. Fletcher, J. A. H. Wass, J. W. Tomlinson, U. Misra, M. Dattani, W. Arlt AV. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency. Anaesthesia. 2020.
6. Lehmann M, Monte K, Barach P, Kindler CH. Postoperative patient complaints: a prospective interview study of 12,276 patients. J Clin Anesth. 2010;22(1):13–21. doi:10.1016/j.jclinane.2009.02.015 PubMed PMID: 20206846.
7. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – A systematic review. Dan Med J. 2018;65(6):1–5. PubMed PMID: 29886882.
8. Freudzon L. Perioperative steroid therapy: Where's the evidence? Curr Opin Anaesthesiol. 2018;31(1):39–42. doi:10.1097/ACO.0000000000000547
9. de Lange DW, Kars M. Perioperative glucocorticosteroid supplementation is not supported by evidence. Eur J Intern Med. 2008;19(6):461–7. doi:10.1016/j.ejim.2007.12.004
10. Miggelbrink LA, Vroom HB, de Keyser CE, Kappen TH, van Klei WA, van Waes JAR. Effects of a supra-physiological corticosteroid regime in surgical patients at risk for tertiary adrenal insufficiency, a retrospective cohort study. Forthcoming.
11. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. European Heart Journal. Oxford University Press; 2022. p. 3826–924. doi:10.1093/eurheartj/ehac270 PubMed PMID: 36017553.
12. Hung KC, Chang LC, Ho CN, Wu JY, Hsu CW, Lin CM, et al. Impact of intravenous steroids on subjective recovery quality after surgery: A meta-analysis of randomized clinical trials. J Clin Anesth. 2024 Dec;99:111625. doi:10.1016/j.jclinane.2024.111625
13. Corcoran TB, Myles PS, Forbes AB, Cheng AC, Bach LA, O'Loughlin E, et al. Dexamethasone and Surgical-Site Infection. N Engl J Med. 2021 May 6;384(18):1731–41. doi:10.1056/NEJMoa2028982 PubMed PMID: 33951362.
14. Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015 Jun 1;100(6):2171–80. doi:10.1210/jc.2015-1218
15. Friedman RJ, Schiff CF, Bromberg JS. Use of supplemental steroids in patients having orthopaedic operations. J Bone Joint Surg. 1995 Dec;77(12):1801–6. doi:10.2106/00004623-199512000-00002

16. Thomason JM, Girdler NM, Kendall-Taylor P, Wastell H, Weddel A, Seymour RA. An investigation into the need for supplementary steroids in organ transplant patients undergoing gingival surgery. J Clin Periodontol. 1999 Sep 9;26(9):577–82. doi:10.1034/j.1600-051X.1999.260903.x
17. Glowniak J V, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery. 1997 Feb;121(2):123–9. doi:10.1016/S0039-6060(97)90280-4
18. Miggelbrink LA, Marsman M, van de Wetering J, van Klei WA, Kappen TH. Perioperative corticosteroid supplementation guideline adherence. Anaesthesia. 2025 Jan 30. doi:10.1111/anae.16556
19. Barker OJH, Ramesh A V, Kangesan I, Barnes J, Harrogate S, Gupta S, et al. Perioperative Replacement of Exogenous Steroids (PREdS): a national audit of current peri-operative prescribing for patients taking therapeutic steroids. Anaesthesia. 2024 Oct;79(10):1042–52. doi:10.1111/anae.16388 PubMed PMID: 39096191.



CHAPTER 8

Dutch guideline to prevent perioperative pulmonal complications.

Lynn Ann Miggelbrink (1), Marije Marsman (1), Jasper R Senff (1), Judith A R van Waes (1), Inez Bronsveld (2), Wilton van Klei (1), Teus Kappen (1)

Department of 1. Anesthesiology, 2. Pulmonology from the University Medical Centre Utrecht, Utrecht University, the Netherlands

Published in Dutch

Ned Tijdschr Geneeskd. 2022 Oct 20:166:D6889.

ABSTRACT

Introduction: Patients with a history of chronic obstructive pulmonary disease (COPD) or asthma undergoing surgery are at risk for developing postoperative pulmonary complications, associated with morbidity and mortality. A national guideline was composed on preventive strategies in non-thoracic surgery, in which perioperative administration of corticosteroids is a cornerstone. We investigated the implementation in our hospital.

Methods: Patients with a history of asthma and/or COPD who underwent non-thoracic surgery between January 2017 and July 2018 in our hospital, were included. Primary outcome was perioperative administration of intravenous prednisolone or oral prednisone as preventative treatment. The reasons for (non)adherence were investigated as secondary outcome.

Results: 1,623 patients qualified for a preventative treatment. Overall, 653 patients (40%) received treatment according to protocol. The other 970 patients received no treatment (79%), another corticosteroid (12%) or received the other strategy (9%). Based on interviews and surveys, several barriers were found: fear of side effects of corticosteroids, indications for other types of corticosteroids, and lack of confidence in the literature.

Conclusion: The current guideline for prevention of postoperative pulmonary complications has not been implemented thoroughly at our hospital. The lack of adherence appears to be caused by lack in clarity in clinical practice, lack of confidence in the evidence on which the protocol is based, and fear of side effects of corticosteroids. There are also notable differences between the vision of pulmonologists and the anesthesiologists. Further research is needed to solidify the guideline, anticipating aforementioned compliance barriers to achieve better implementation.

INTRODUCTION

Perioperative pulmonary complications (PPCs) occur frequently and contribute to postoperative morbidity and mortality, and contribute to a prolonged hospital readmission as well as hospital admissions.(1–3) The most important PPCs are atelectasis, bronchospasm, and pulmonary infections.(5,6) The PPC incidence varies per study population but can reach up to 75 percent.(1,4) Patients with chronic obstructive pulmonary disease (COPD), or asthma have an increased risk for PPC such as an exacerbation of the existing pulmonary disease. This risk increases as the underlying pulmonary disease is worse.(4,7,8) Specific types of surgical procedures (i.e. thoracic, upper abdominal, vascular, head and neck surgery) also increase the risk of PPCs.(5) Other risk factors are emergency surgery, prolonged surgical duration, and general anesthesia. (9)

Several studies have investigated pharmacological treatments for the prevention of PPCs. Several small studies investigated the effect of systemic corticosteroids on PPC after surgery and reported a lower risk of PPCs.(10–13) These reports were included in 2012 in a consensus based national multidisciplinary guideline advising the use of corticosteroids for PPC prevention in patients with asthma or COPD.(14) The guidelines recommends a combination of sympathomimetic and anticholinergic inhalation medication with systemic corticosteroids for prevention of PPCs. Patients with stable and mild pulmonary disease, intravenous administration of prednisolone is advised at the induction of anesthesia and 12 hours after the first dose (Protocol A)(Figure 1). For patients with more severe or unstable COPD or asthma, it is recommended to start oral prednisone three days preoperatively (Protocol B)(Figure 1).(14) The type of anesthesia (e.g. general or locoregional anesthesia) does not affect these recommendations, although the guideline does recommend locoregional anesthesia for the prevention of PPCs, as it is associated with a lower risk of PPCs.

This is a national guideline, which does not exist in any form in other countries. In daily practice, we also observed that there was a lot of criticism of this protocol within our own group. Therefore, we investigated the implementation rate of the guideline in a university medical center by quantifying adherence to the protocol in a cohort of patients who, according to the guideline, had an indication for preventive treatment with corticosteroids (Protocol A or B). Subsequently, interviews and

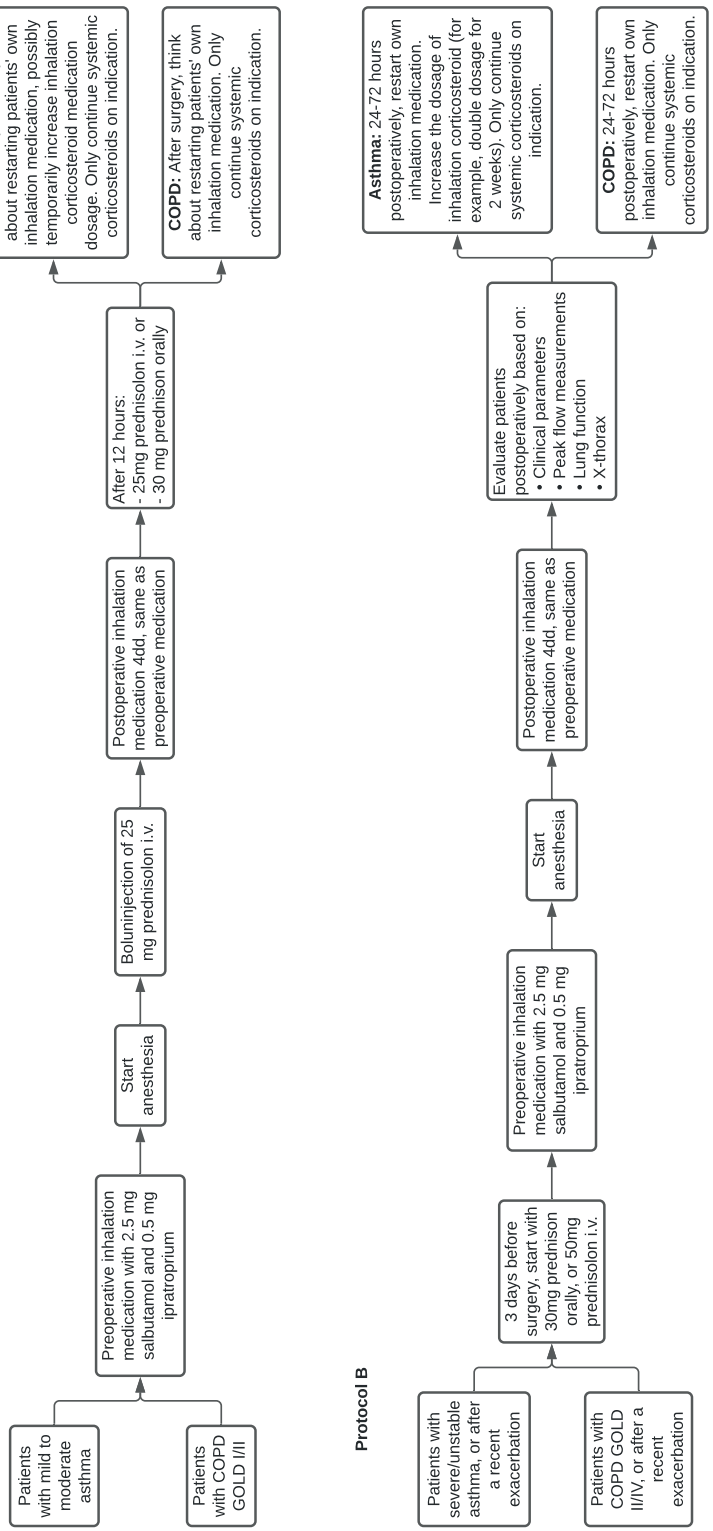


Figure 1. Lung protocol A or B

surveys were conducted among anesthesiologists and pulmonologists to identify barriers to implementation.

METHODS

Study design and population

This study consisted of two parts. First, we assessed the adherence the Dutch guideline to prevent PPCs in patients with asthma or COPD by anesthesiologists. This was investigated using a retrospective, single-center cohort which included patients with asthma or COPD undergoing non-thoracic elective surgery between January 2017 and July 2018 at the UMC Utrecht under general or locoregional anesthesia. Patients admitted to the Intensive Care Unit before surgery or those undergoing thoracic surgical procedures were excluded. All patients visited the preoperative assessment clinic at our hospital. All included patients had an indication for a preventative treatment (Protocol A or B), which should have been prescribed (Protocol B) or administered in the operating room (Protocol A). Using the electronic patient record, it was quantified in how many patients this occurred. In the second part of the study, anesthesiologists were interviewed to identify the barriers to guideline adherence. The main themes emerging from the interviews were used to create surveys, which were sent to all anesthesiologists (in training) and all pulmonologists (in training) at UMC Utrecht. The aim of the surveys was to validate the key findings from the interviews in a larger group of anesthesiologists and pulmonologists, and to compare opinions on the use of the lung protocols between the two specialties.

The medical ethics review board of UMC Utrecht assessed the study as not subject to the WMO (Medical Research Involving Human Subjects Act).

Data collection

The data were gathered retrospectively and anonymously from the hospital electronic record systems (HiX, Chipsoft, The Netherlands, and Anstat, Carepoint, The Netherlands). Data obtained included patient characteristics, i.e. sex, age, body mass index, medical history, type and duration of surgery, and type of anaesthesia. If the severity of the pulmonary disease was not documented, the severity was assessed in retrospect based on lung function tests and pulmonary symptoms. If this data was unavailable, patients were pragmatically considered to have mild pulmonary disease, as severe conditions were likely to be documented.

Patients were divided into two groups: patients who should have received protocol A according to the guideline, and patients who should have received protocol B. Patients in the protocol A group should have received 25 mg prednisolone intravenously during induction of anaesthesia. Prednisolone administered within 30 minutes after induction was noted as protocol adherence. Patients in the protocol B group should have received a prescription of oral prednisone 30 mg daily, starting three days prior to surgery (Table 1, Figure 1).

Outcome

Documentation of administered inhalation medication (protocol A and B) was unreliable because patients often manage this themselves. Therefore, the primary outcome of protocol adherence was defined as the prescription of oral corticosteroids at the preoperative assessment clinical (protocol B), or administration of prednisolone during surgery (protocol A). Patients who did not corticosteroids according to a lung protocol (protocol A or B), were classified as "non-adherence to protocol". If patients received another type of corticosteroid in the operating room, this was also categorized as non-adherence. However, since the attending anesthesiologist may have considered another type of corticosteroid as a valid alternative to prednisolone, these cases were categorized in a separate category.

Statistical analyses

Patients were analyzed according to the indication for Protocol A or B. Categorical data were described as absolute numbers (N) and frequencies (%). Continuous data were described as means with standard deviations (SD), or median with interquartile ranges (IQR) where appropriate. Normality was tested using the Kolmogorov-Smirnov test. Data were analyzed using IBM SPSS Statistics 25.0 software (IBM, Armonk, NY).

Implementation barriers

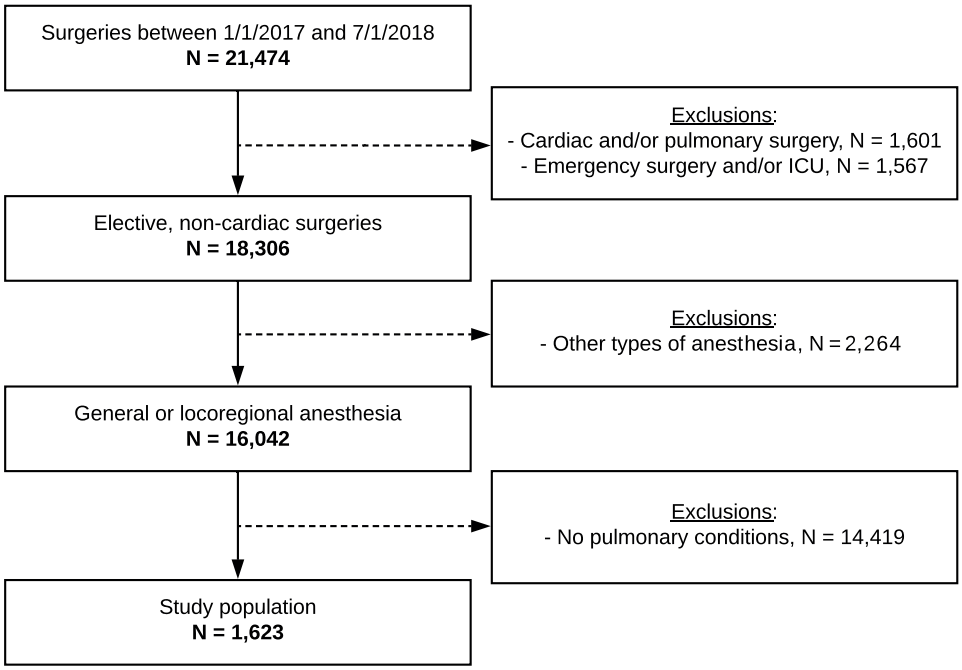
Barriers to implementation of the guideline were investigated using semi-structured interviews and questionnaires. Anesthesiologists were randomly selected and interviewed (by author LAM) on their views on the guideline and reasons for (non-)adherence. The number of interviews was not predetermined; interviews continued until data saturation was reached. Saturation was defined as the point at which no new reasons for (non-)adherence were mentioned over two consecutive interviews. Interviews were recorded and subsequently transcribed.

The transcribed text was analyzed using open coding, followed by classification of main themes. The observed reasons identified for (non-) adherence to the guideline were then used to formulate several example cases for use in a survey. The survey aimed to assess whether clinicians would recommend and/or administer corticosteroids in specific scenarios and to validate the reasons for (non-)adherence identified during the interviews. The survey was distributed to pulmonologists (in training) and anesthesiologists (in training). All data were analyzed anonymously.

RESULTS

Of the 1,623 included patients (Figure 2), 892 (55%) had asthma and 731 (45%) had COPD. The median age was 61 years (IQR 49–70), and 54% were female. Patient characteristics are shown in Table 1. All 1,623 patients were indicated to receive a lung protocol (protocol A or B) according to the guideline. In 943 patients (58%), a lung protocol was recommended at the preoperative assessment clinic (Protocol A or B), while in 42%, the guideline was not followed at the preoperative assessment clinic (Figure 3). In 855 patients (53%), the protocol was recommended according to the indication specified in the guideline.

Figure 2. Flowchart



Corticosteroids were administered in 653 patients (40%). There were 767 patients (47%) who did not receive any treatment, 119 patients (7%) who received a different corticosteroid, and 84 patients (5%) who were treated according to the other lung protocol (i.e., Protocol B instead of A, or vice versa).

A total of 1,511 patients were eligible for Protocol A, of whom 582 (39%) received corticosteroids according to Protocol A. Protocol B was indicated in 112 patients, of whom 71 (63%) were treated according to the guideline. Most patients for whom Protocol B were indicated but who did not receive it were treated instead with Protocol A (Figure 3).

Table 1. Baseline characteristics

		Strategy A		Strategy B	
		Indicated, treated accordingly N = 582	**Indicated, not treated accordingly**[1] N = 929	**Indicated, treated accordingly** N = 71	**Indicated, not treated accordingly**[1] N = 41
Asthma, N (%)	Mild	220 (38)	539 (58)	0 (0.0)	0 (0.0)
	Moderate	58 (10)	56 (6.0)	0 (0.0)	0 (0.0)
	Severe/Unstable	0 (0.0)	0 (0.0)	8 (10)	11 (2)
COPD, N (%)	GOLD I	140 (24)	177 (19)	0 (0.0)	0 (0.0)
	GOLD II	151 (26)	144 (16)	0 (0.0)	0 (0.0)
	GOLD III	0 (0.0)	0 (0.0)	45 (63)	27 (66)
	GOLD IV	0 (0.0)	0 (0.0)	14 (10)	3 (7.3)
	Unstable COPD	0 (0.0)	0 (0.0)	3 (4.2)	0 (0)
	Missing	*13 (2.2)*	*13 (1.4)*	*1 (1.4)*	*0 (0)*
Inhalation medication, N (%)	Any kind [2]	468 (80)	569 (61)	63 (89)	36 (87)
	Steroid [3]	331 (57)	426 (46)	47 (66)	25 (61)
ASA, N (%)	1	3 (0.5)	49 (5.3)	0 (0)	0 (0)
	2	335 (58)	576 (62)	6 (8.5)	10 (24)
	3	239 (41)	290 (31)	50 (70)	29 (71)
	4	5 (0.9)	14 (1.5)	15 (21)	2 (4.9)
Smoking, N (%)	Former	214 (37)	280 (30)	38 (54)	17 (42)
	Current	200 (34)	222 (24)	24 (34)	16 (39)

Table 1. Continued

		Strategy A		Strategy B	
		Indicated, treated accordingly N = 582	**Indicated, not treated accordingly**[1] N = 929	**Indicated, treated accordingly** N = 71	**Indicated, not treated accordingly**[1] N = 41
	Missing	*0 (0.0)*	*1 (0.1)*	*0 (0)*	*0 (0)*
Admission type, N (%)	Inpatient	490 (84)	645 (69)	67 (94)	30 (73)
Surgery type, N (%)	Orthopaedic	34 (5.8)	99 (11)	7 (9.9)	3 (7.3)
	Uro-genital	88 (15)	166 (18)	13 (18)	5 (12)
	Vascular	50 (8.6)	46 (5.0)	10 (14)	3 (7.3)
	Head and neck	208 (36)	247 (27)	25 (35)	18 (44)
	General	98 (17)	88 (9.5)	7 (9.9)	4 (9.8)
	Other	104 (18)	283 (31)	9 (13)	8 (20)
Anesthesia type, N (%)	General	547 (99)	807 (87)	60 (85)	40 (98)
	Spinal	6 (1.0)	89 (9.6)	10 (14)	0 (0.0)
	Peripheral nerve block	2 (0.3)	33 (3.6)	1 (1.4)	1 (2.4)
Surgery duration, N (%)	≥ 2 hours	302 (52)	363 (39)	35 (49)	15 (37)

ASA, American Society of Anesthesiologists physical status classification system; COPD, Chronic Obstructive Lung Disease; GOLD, Global Initiative for Obstructive Lung Disease; IQR, Interquartile range; kg, kilograms; m, meters

[1] Including patients receiving no corticosteroids, other types of corticosteroids or the other strategy

[2] The percentage represents patients who use any type of inhalation medication at home

[3] The percentage of patients who use steroid inhalation medication of the patients who use inhalation medication

Figure 3. Flow diagram steps to adherence

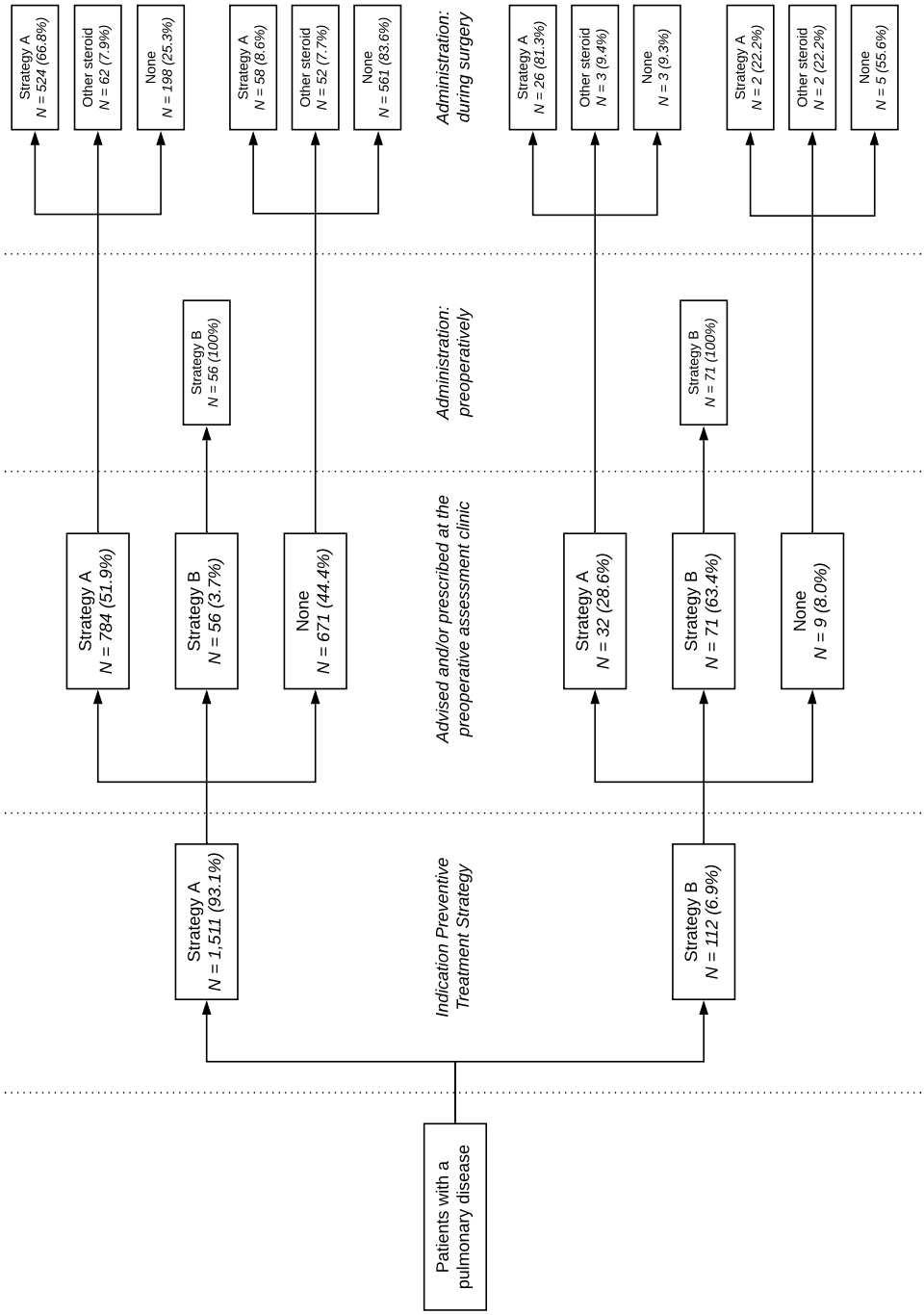


Table 3. Results surveys in comparison to observed daily practice

Strategy indicated	**Question**	**Answer**	**Survey** (anesthesia)	**Survey** (pulmonology)	**Daily practice** [2] (anesthesia)
Context: general anesthesia					
A	Patient with COPD GOLD 2. What would you administer?	According to strategy A	95%	100%	40%
		Another type of corticosteroid	-	-	12%
A	Patient with COPD GOLD 2, and indication for PONV prophylaxis. What would you administer?	Administer strategy A	63%	-	-
		Administer PONV prophylaxis [3]	30%	20%	-
		Administer both strategy A and PONV prophylaxis [3]	5%	78%	-
	- *Reasons for administration of strategy A?*	- *Prednisolone also acts as PONV prophylaxis*	28%	-	-
		- *Prevention of pulmonary complications*	54%	-	-
		- *Advice from the preoperative assessment clinic*	27%	-	-
	- *Reasons for administration of dexamethasone?*	- *Dexamethasone also acts as strategy A*	79%	-	-

Table 3. Continued

Strategy indicated	**Question**	**Answer**	**Survey** (anesthesia)	**Survey** (pulmonology)	**Daily practice** [2] (anesthesia)
		– *Only PONV prophylaxis*	7%	–	–
		According to strategy B	28%	–	–
A	Reaction pulmonologist when anesthesiologist deviates from advice after consultation, administering only PONV prophylaxis[3] during surgery.	Call anesthesiologist for consultation and/or discussion	–	60%	–
		PONV prophylaxis is enough	–	20%	–
		Nothing	–	20%	–
B	Patient with COPD GOLD 3. What was administered?	In concordance of strategy B	85%	90%	63%
B	Patient with COPD GOLD 3. Prednisone not prescribed at the preoperative assessment clinic. What was administered during surgery?	In concordance of strategy A	93%	–	68%
	– *Reasons for administration strategy A?*	– *Strategy A is enough*	*15%*	–	–
		– *Too late for strategy B*	*73%*	–	–

Table 3. Continued

Strategy indicated	**Question**	**Answer**	**Survey** (anesthesia)	**Survey** (pulmonology)	**Daily practice** [2] (anesthesia)
Context: loco-regional anesthesia					
A	Patient with COPD GOLD 1 in a patient with insulin dependent diabetes mellitus. What was administered?	In concordance of strategy A	28%	60%	6%
	– *If strategy A not administered, why?*	– *Not necessary in loco-regional anesthesia*	72%	–	–
		– *Undesirable effects*	44%	–	–

[1] Strategy A: 25 mg of prednisolone intravenously during start of surgery; Strategy B: 30 mg of prednisone orally starting 3 days prior to surgery

[2] Based on data from table 2

[3] 4 mg dexamethasone

COPD, Chronic Obstructive Pulmonary Disease; PONV, postoperative nausea and vomiting

Implementation barriers

Interviews

Five anesthesiologists and three residents were interviewed to determine reasons for (non-)adherence to the protocol. Most reported they would follow protocol, and although some believed that the guideline is based on only a limited number of studies, none indicated that they would ignore the protocol. Not all considered the administration of corticosteroids useful for the prevention of PPCs in patients with mild lung disease. Concerns were raised regarding corticosteroid side effects, such as delayed surgical wound healing or glycemic disturbances in patients with diabetes. The main themes identified for non-adherence to the guideline are presented in Appendix 1.

Surveys

The survey was completed by 19 anesthesiology residents and 21 anesthesiologists (54% of the 74 anesthesiologists to whom it was sent). Among respondents, 95% indicated that they would administer Protocol A to patients undergoing elective surgery under general anesthesia, provided there were no (relative) contraindications. However, only 54% of anesthesiology respondents believed that corticosteroids could prevent a PPC. Despite this, 46% of respondents reported that they would still administer corticosteroids in the operating room if it had been recommended at the anesthesiology outpatient clinic. Additionally, 44% of respondents generally felt that the benefits of corticosteroids (risk reduction of PPCs) did not outweigh the potential side effects.

In a case example of a patient with diabetes undergoing a procedure under locoregional anesthesia, only 28% of anesthesiologists indicated that they would follow the guideline, while 72% expressed uncertainty about the usefulness of corticosteroids in this scenario. Reasons cited included the negative effect of corticosteroids on glucose regulation and the assessment that the risk of PPCs with locoregional anesthesia is lower than with general anesthesia, making the potential harms of corticosteroids outweigh the benefits.

Dexamethasone is often administered perioperatively in certain types of surgery, such as joint replacement or neurosurgery, or for the prevention of postoperative nausea and vomiting (15–17). In a case example of a patient with COPD who also had an indication for dexamethasone, 63% of anesthesiologists reported that they would prefer to administer

prednisolone instead of dexamethasone. Among the anesthesiologists who would choose dexamethasone as first-line, 79% believed that dexamethasone would also reduce the risk of PPCs.

In a case example of a patient who should be treated according to Protocol A but for whom a pulmonologist recommended Protocol B, 68% of anesthesiologists reported that they would still treat the patient according to Protocol A.

In a case example of a patient with an indication for Protocol B according to the guideline, most anesthesiologists (85%) reported that they would follow this recommendation. However, if Protocol B had not been prescribed at the preoperative assessment clinic, 93% of anesthesiologists reported that they would pragmatically choose Protocol A as an alternative on the day of surgery. Some would also consult the pulmonologist postoperatively. Anesthesiologists and pulmonologists generally agreed on the indication for Lung Protocol B (85% and 90%, respectively).

The survey was completed by 10 pulmonologists (63% of those approached), of whom 7 were in training. In a case example of a patient with an indication for Protocol A according to the guideline, 100% of pulmonologist respondents would recommend Protocol A if the patient underwent general anesthesia, but only 60% would recommend it for a procedure under locoregional anesthesia. Most pulmonologists recommended administering both prednisolone and dexamethasone (80%) if there were multiple indications for corticosteroids.

Two ad-hoc observations were made. First, pulmonologists reported that they believed better collaboration between the pulmonology and anesthesiology departments would likely reduce PPCs. They suggested that pulmonologists should be consulted for all patients with pulmonary comorbidities undergoing surgery. Second, pulmonologists stated that they also considered the degree of bronchial hyperreactivity in their decisions regarding PPC prevention. This was their main reason for prescribing Protocol B instead of the guideline-recommended Protocol A. The results of the surveys and observations in daily practice for both the anesthesiology and pulmonology departments are presented in Table 2.

In the sample case of a patient with an indication for strategy B, most anesthesiologists would adhere to protocol (85%). In patients with an

indication for strategy B who did not start treatment three days prior to surgery, 93% of physicians would administer corticosteroids in accordance with strategy A. Some would also ask the pulmonologist for a postoperative consultation. Anesthesiologists and pulmonologists mostly agree on strategy B and would administer corticosteroids in most cases (85% and 90% respectively).

DISCUSSION

We investigated the local implementation of the national guideline for the prevention of perioperative pulmonary complications regarding corticosteroid administration. Among patients for whom the guideline recommends corticosteroids on the day of surgery (Protocol A), only 39% were treated according to the protocol. For patients indicated for longer preoperative corticosteroid preparation (Protocol B), 63% were treated according to the protocol. A survey of the professionals involved, indicated a high intention to follow the guideline, but real-world data show that actual implementation in daily practice lags. For Protocol A, adherence in practice was much lower than suggested by the survey (39% versus 95%). The discrepancy was also present for Protocol B, though less pronounced (63% versus 85%).

To our knowledge, this is the first study to investigate the implementation of the guideline for the prevention of PPCs in patients with chronic lung disease through corticosteroid administration. The combined results of observed adherence, interviews, and surveys suggest several possible explanations for non-adherence to the guideline by anesthesiologists. First, the guideline does not sufficiently align with the thought process of anesthesiologists when deciding whether or not to administer prednisone. Anesthesiologists indicated that concerns about hyperglycemia and wound healing influenced their decisions, particularly in patients they considered at high risk. The guideline does not clarify whether these considerations are justified. Implementation was also influenced by the use of locoregional anesthesia, for both pulmonologists and anesthesiologists. Again, the guideline provides little evidence or guidance on whether this consideration is appropriate.

In addition, the guideline does not provide advice on whether an alternative corticosteroid, such as dexamethasone given for the prevention of nausea, could be considered an equivalent substitute.

Second, anesthesiologists reported that their decisions were influenced by uncertainty regarding the effectiveness of corticosteroids for PPC prevention, as the guideline recommendations are based on limited evidence. Only a handful of (often very small) randomized trials have been conducted in which patients received corticosteroids.(10,13,18,19) Other studies were conducted retrospectively.(11,20) Although most studies suggest a positive effect as part of a bundle of preventive measures, the studies are too small and/or heterogeneous to allow for a reliable meta-analysis. Finally, a combination of the first two points may influence adherence to the guideline: the lack of robust scientific evidence did not convince anesthesiologists that the potential benefit outweighs the possible side effects of corticosteroids.

The observed potential explanations for non-adherence are also reflected in the differences in perspective between pulmonologists and anesthesiologists. Anesthesiologists are less likely than pulmonologists to administer two types of corticosteroids when there is an indication for dexamethasone to prevent postoperative nausea and vomiting, and an indication for prednisolone to prevent PPCs according to the guideline (5% versus 78%). Anesthesiologists are also less likely to administer prednisolone to patients with diabetes mellitus undergoing surgery under locoregional anesthesia compared with pulmonologists (28% versus 60%). The most notable difference between anesthesiologists and pulmonologists, based on an ad-hoc observation, was the administration of Protocol B to patients with moderately severe asthma. While most anesthesiologists would administer Protocol A according to the guideline, pulmonologists reported that they take the presence of bronchial hyperreactivity into account in their recommendations and would prescribe Protocol B. Our results therefore strongly suggest that the guideline provides insufficient guidance for several decisions that are common in daily clinical practice.

Due to the retrospective nature of the study, several assumptions had to be made. First, only the intravenous administration of prednisolone was considered “in accordance with the protocol” for Protocol A. This choice was made pragmatically, as it was not possible to determine the reasons for administering other types of corticosteroids. The survey indicated that anesthesiologists believed that other corticosteroids could be equally effective in preventing PPCs. To our knowledge, no studies have primarily compared different classes of corticosteroids and their effects on the prevention of pulmonary complications. One study that investigated the

effects of methylprednisolone and dexamethasone showed comparable efficacy and side effects.(21) Therefore, it seems reasonable to assume that different types of corticosteroids may have the same effect in preventing PPCs. Second, it was not possible to determine from the data whether other corticosteroids administered during induction were given as preventive treatment or for another indication. The protocol was considered "adhered to" if the patient received prednisolone, while other types of corticosteroids were classified as "not treated according to protocol." However, the survey indicated that anesthesiologists believed that other corticosteroids could be equally effective in preventing PPCs in patients with an indication for alternative corticosteroids. Additionally, it was assumed that patients who received corticosteroids according to the protocol, also took their inhalation medication. This assumption may have led to an overestimation of guideline implementation. It was also assumed that patients who were instructed to start prednisone at home three days before surgery actually did so. Finally, the survey revealed a discrepancy with the observations. Although this may result from socially desirable responses or an overestimation of individual performance, it may also reflect differences between the patients described in the survey and the actual population at our hospital. This could lead to an overestimation of protocol adherence.

Implementation of guidelines is challenging.(22–24) Implementing a guideline based on consensus without substantial evidence can be even more difficult, as it may receive less support from professionals who must apply it in daily practice. Several studies have investigated protocol adherence and reported similar barriers to guideline implementation: a lack of evidence for the recommendations, insufficient specification of how the guideline applies to the complexity of daily practice, and a lack of explanation or rationale behind the recommendations.(22,23,25–27) Katz et al. concluded that insufficient evidence is an important factor in guideline implementation. Moreover, a guideline based solely on literature support may not be sufficient for effective implementation.(28) Baron et al. summarized the factors that improve guideline implementation as follows: guidelines should be based on high-quality evidence, they should align with the patients and situations that clinicians encounter in daily practice, and clinicians should understand the rationale behind the recommendations.(29) Tickell et al. found that non-adherence to guidelines correlates with individualized care for patients who fall outside the patient population described in the guideline.(30) Volovici reported similar findings and identified the unique patient—whose

characteristics are not addressed by the protocol—as the main barrier to implementation.(31)

CONCLUSION

This study demonstrates that the local implementation of the national guideline for the prevention of perioperative pulmonary complications is moderately successful with regard to corticosteroid administration in patients with asthma or COPD. Anesthesiologists appear more willing to administer corticosteroids to patients with more severe lung disease. Non-adherence to the guideline seems to result from insufficient guidance for specific patients, as well as a lack of supporting literature, particularly in cases of locoregional anesthesia.

Notable differences were also observed between the perspectives of pulmonologists and anesthesiologists, even though both groups were involved in developing the guideline. Implementation could be improved either through prospective interventional research to address points of debate, or by revising the guideline to include additional information and considerations tailored to specific clinical circumstances.

REFERENCES

1. Mohr DN, Lavender RC. Preoperative pulmonary evaluation Identifying patients at increased risk for complications. Postgrad Med. 1996;100(5):241–56.
2. Lakshminarasimhachar A, Smetana GW. Preoperatieve Evaluation: Estimation of Pulmonary Risk. Anesthesiol Clin. 2016;34:71–88.
3. Sabate S, Mazo V, Canet J. Predicting postoperative pulmonary complications : implications for outcomes and costs. Curr Opin Anaesthesiol. 2014;27:201–9.
4. Kips JC. Preoperative pulmonary evaluation. Acta Clin Belg. 1997;52(5):301–5.
5. Yang CK, Teng A, Lee DY, Rose K. Pulmonary complications after major abdominal surgery: National Surgical Quality Improvement Program analysis. J Surg Res. 2015;198:441–9.
6. NAEPP Coordinating Committee. National Asthma Education and PreventionProgram (NAEPP): Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services. 2010. p.17–53. Available from: https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthgdln_1.pdf
7. Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable Predictors of Postoperative Respiratory Failure after General and Vascular Surgery: Results from the Patient Safety in Surgery Study. J Am Coll Surg. 2007;204(6):1188–98.
8. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000;232(2):242–53.
9. Lawrence VA, Cornell JE, Smetana GW. Strategies To Reduce Postoperative Pulmonary Complications after Noncardiothoracic Surgery : Systematic Review for the American College of Physicians. Ann Intern Med. 2006;144:596–608.
10. Bingol H, Cignoz F, Balkan A, et al. The Effect of Oral Prednisolone with Chronic Obstructive Pulmonary Disease Undergoing Coronary Artery Bypass Surgery. J Card Surg. 2005;20:252–6.
11. Kabalin CS, Yarnold PR, Grammer LC. Low complication rate of corticosteroid-treated asthmatics undergoing surgical procedures. Arch Intern Med. 1995;155:1379–84.
12. Mitsuta K, Shimoda T, Fukushima C, et al. Preoperative Steroid Therapy Inhibits Cytokine Production in the Lung Parenchyma in Asthmatic Patients. Chest. 2001;120(4):1175–83.
13. Silvanus M-T, Groeben H, Peters J. Corticosteroids and Inhaled Salbutamol in Patients with Reversible Airway Obstruction Markedly Decrease the Incidence of Bronchospasm after Tracheal Intubation. Anesthesiology. 2004;100:1052–7.
14. Nederlandse Vereniging voor Anesthesiologie. Richtlijn Preventie van perioperatieve pulmonale complicaties bij niet-pulmonale chirurgie bij patienten met een verhoogd risico op pulmonale complicaties. 2012. p. 1–121. Available from: https://www.anesthesiologie.nl/uploads/files/KD_RL_Preventie_pulmonaal_belaste_patient_2012.pdf
15. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118(1):85–113.
16. Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: An update. Neuro-Oncology Pract. 2015;2(1):6–12.

17. Yue C, Wei R, Liu Y. Perioperative systemic steroid for rapid recovery in total knee and hip arthroplasty: A systematic review and meta-analysis of randomized trials. J Orthop Surg Res. 2017;12(1):1–11.
18. Stein M, Cassara EL. Preoperative Pulmonary Evaluation and Therapy for Surgery Patients. JAMA. 1970;211(5):787–90.
19. Starobin D, Kramer MR, Garty M, Shitirt D. Morbidity associated with systemic corticosteroid preparation for coronary artery bypass grafting in patients with chronic obstructive pulmonary disease: a case control study. J Cardiothorac Surg. 2007;6:1–6.
20. Lee HW, Lee JK, Oh SH, et al. Effect of perioperative systemic steroid treatment on patients with obstructive lung disease undergoing elective abdominal surgery. Clin Respir J. 2018;12(1):227–33.
21. Ardestani ME, Kalantary E, Samaiy V, Taherian K. Methyl prednisolone vs Dexamethasone in Management of COPD Exacerbation; a Randomized Clinical Trial. Emergency. 2017;5(1):1–6.
22. Baron DM, Metnitz PGH, Fellinger T, et al. Evaluation of clinical practice in perioperative patient blood management. Br J Anaesth. 2016;117(5):610–6.
23. Hoeks SE, Scholte Op Reimer WJM, Lenzen MJ, et al. Guidelines for cardiac management in noncardiac surgery are poorly implemented in clinical practice: Results from a peripheral vascular survey in The Netherlands. Anesthesiology. 2007;107(4):537–44.
24. Tierney WM, Overhage M, Takesue BY, et al. Computerizing guidelines to Improve Care and Patient Outcomes: The Example of Heart Failure. JAMIA. 1995;2:316–22.
25. St. Clair CM, Shah M, Diver EJ, et al. Adherence to evidence-based guidelines for preoperative testing in women undergoing gynecologic surgery. Obstet Gynecol. 2010;116(3):694–700.
26. Jackson MJ, Patvardhan C, Wallace F, et al. Perioperative management of diabetes in elective patients: A region-wide audit. Br J Anaesth. 2016;116(4):501–6.
27. Woolard AA, Ehrenfeld JM, Eagle SS, Wanderer JP. A retrospective study showing the extent of compliance with perioperative guidelines in patients with coronary stents with regard to double antiplatelet therapy. J Clin Anesth. 2016;33:179–84.
28. Katz DA. Barriers Between Guidelines and Improved Patient Care: An Analysis of AHCPR's Unstable Angina Clinical Practice Guideline. HSR Heal Serv Res. 1997;34(1):377–89.
29. Baron DM, Metnitz PGH, Rhodes A, Kozek-langenecker SA. Clinical guidelines: How can we improve adherence and implementation ? Eur J Anaesthesiol. 2017;34:329–31.
30. Tickell KD, Mangale DI, Tornberg-Belanger SN, et al. A mixed method multi-country assessment of barriers to implementing pediatric inpatient care guidelines. PLoS One. 2019;14(3)
31. Volovici V, Ercole A, Citerio G, Stocchetti N, et al. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. World Neurosurg. 2019;125:e515–20.

SUPPLEMENTARY FILES

S1. Themes following quantitative analysis of transcribed interviews

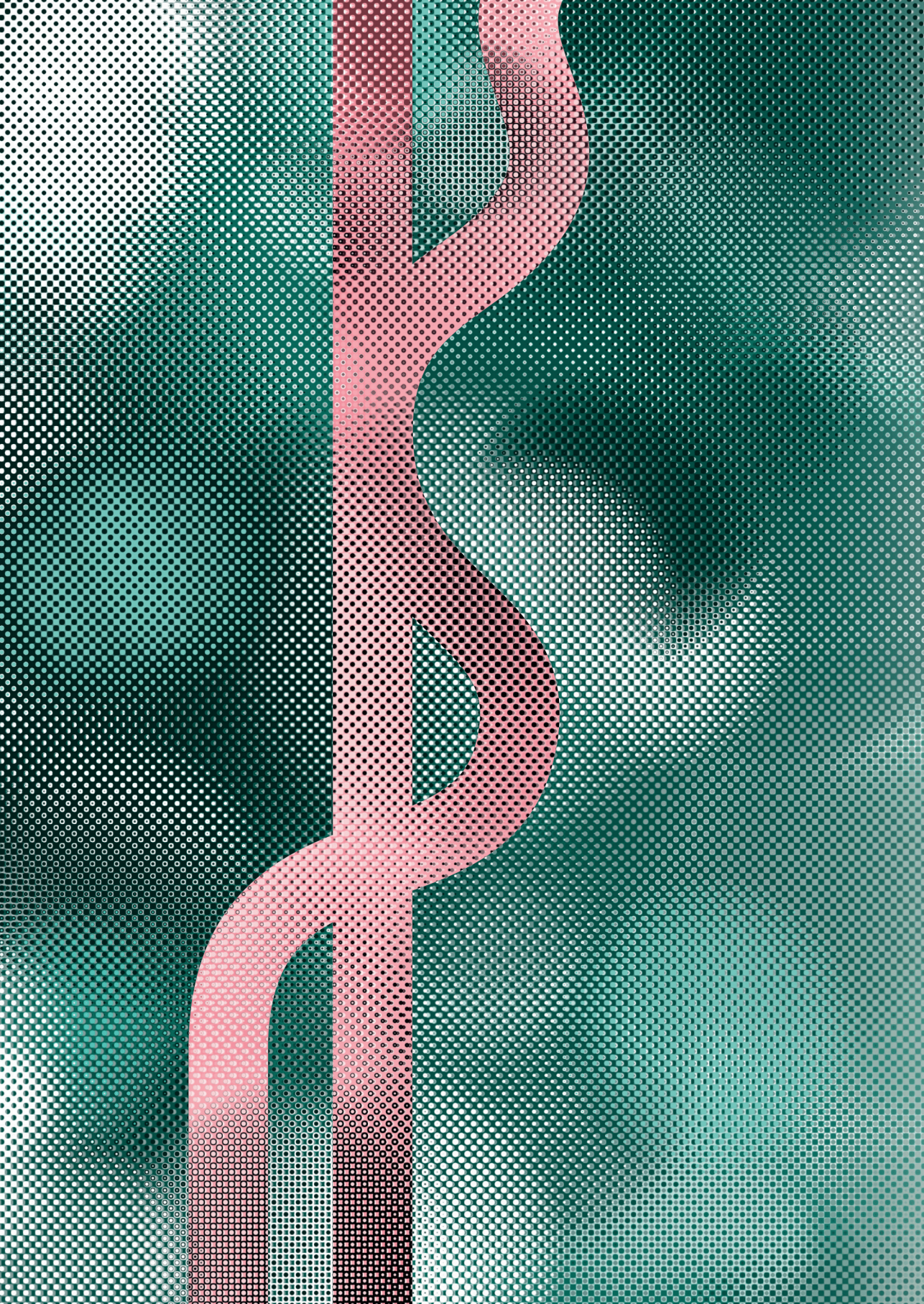
Main theme	Quotes (translated from Dutch)
Reasons for adherence:	
Patients with an indication for protocol A who receive protocol A. However, repetition of administration after 12 hours often forgotten.	"When patients are undergoing a low risk, outpatient surgery, then I doubt the feasibility of the repetition of administration of prednisone."
Patients with an indication for protocol B often receive protocol B.	"I write a prescription, though often after consulting their own pulmonologist."" "I almost always prescribe prednisone in patients with an indication for protocol B."
Reasons for non-adherence:	
Mild and or small operations often do not receive protocol A.	"In patients with stable and mild COPD or asthma undergoing minor surgery, I often don't administer prednisone". "Sometimes I will forget it. Sometimes, especially when I am in doubt, I will not administer it for patients undergoing outpatient surgery.
Side effects, especially in patients with comorbidities.	"Sometimes the administration of corticosteroids feels like overshoot. Other times it is too much, especially in some types of patients. Our population consists of a lot of diabetics. Their glucose levels will be altered by corticosteroid. It can even lead to problems of healing of wound." "There are times I will consciously deviate from protocol, i.e. in patients with diabetes or patients with a known bipolar disorder with an indication for protocol B."
Not convinced based on literature.	"There is little literature on the preventive protocols, and all studies are small. There is however a lot of evidence about side effects of corticosteroids, which is why I will always consider administration of steroids critically." "There is little evidence for preventive lung treatments. The literature on which the protocol is based, is very limited..... I think that the proof is limited and I am not convinced of the effect."
Difficult to follow protocol due to difficult protocol. Not always known that an indication is present.	"Sometimes the vast amount of protocols, but also the amount of information in protocols, is overwhelming, and then you forget it." "I am not at the preoperative assessment clinic very often, and then I need to really look into the protocol again. I find the protocol difficult to follow."

S1. Continued

Main theme	Quotes (translated from Dutch)
Prednisone should not be given extra when other type of corticosteroid has already been administered.	"When another type of corticosteroid is indicated based on the type of surgery or as PONV prophylaxis, I often administer another type of corticosteroid, usually dexamethasone. I don't administer extra prednisone, this would be overkill." "I don't expect much difference between different types of corticosteroids. I will administer dexamethasone or hydrocortisone, in which it also serves as preventive treatment.
Themes not included in surveys	
Not feeling like a practicing doctor when only allowed to follow protocols.	"Sometimes you do not feel like a doctor when you're only following the diagrams. If you look at it like a physician, you will probably administer corticosteroids anyways."
Pragmatic approach in patients who smoke excessively, often receiving protocol A.	"Sometimes when patients do not have a diagnosis yet, but I think they must have underlying lung disease (i.e. COPD), I will advise administration of protocol A pragmatically."



PART III
GENERAL DISCUSSION



CHAPTER 9

General Discussion

REFLECTION ON RESEARCH AND MAIN FINDINGS

Perioperative medicine continues to face persistent knowledge gaps. Even when clinical guidelines and protocols exist, they are often based on limited evidence, and clinicians frequently rely on expert opinion or personal experience. This thesis aimed to address some of these gaps and investigated the perioperative management of two medications frequently used by patients undergoing surgery, including renin-angiotensin system inhibitors (RASi) and corticosteroids. In addition to the research findings, this work also highlights challenges in the conduct of clinical research, and the implementation of research results in perioperative medicine, such as logistical, organizational, and communication barriers. In this chapter the studies and relevance of the findings for clinical practice will be shortly addressed. The rest of the chapter will focus on the challenges we encountered and learned from during these studies.

RASi are often used chronically to treat hypertension. Both perioperative continuation as well as discontinuation, have their own potential risks. The lack of convincing evidence leads to varying practices among hospitals and individual physicians.(1,2) We therefore attempted a randomized clinical trial to investigate the effect of continuation versus discontinuation of RASi on the incidence of postoperative kidney injury. Unfortunately, early study termination was necessary due to slow inclusion rates, and definitive conclusions regarding the best strategy around surgery (continuation or discontinuation) could not be drawn (chapters 2 and 3).(3) In a small sub study, we investigated adherence to the instructions about intake of RASi through measurements of the medication levels in blood. Not all patients seemed to have adhered to these instructions, despite extensive verbal and written instructions. Reasons for non-adherence remain unclear, as the results did not correspond with the diary patients kept about the intake of their RASi (chapter 4). Medication adherence in general has been studied extensively, as well as interventions aimed at improving adherence, although these have shown only modest effects.(4–6) However, adherence to randomization or perioperative medication instructions within the context of a clinical trial has been less thoroughly investigated, particularly in patients undergoing surgery. This represents an important gap in the literature, and further research into this phenomenon seems warranted. In addition, one could argue that if medication instructions are not followed reliably, even within the structured setting of a clinical trial, this raises the question of the practical value of issuing such instructions in routine clinical care.

Moreover, given that no clear beneficial effect of discontinuing RASi has been demonstrated to date, there is an even stronger justification for advising patients to continue their usual medication regimen, with the exception of anticoagulants.

Corticosteroids are often prescribed for treatment of autoimmune, inflammatory and pulmonary diseases. However, chronic usage may lead to adrenal insufficiency. In severe cases, corticosteroid induced adrenal insufficiency (e.g. tertiary adrenal insufficiency), may lead to perioperative hemodynamic instability.(7,8) To prevent possible complications, it is recommended to administer supplemental doses of glucocorticoids to patients on these medications, even though the quality of the evidence is low.(9) In our study investigating adherence to the Dutch national protocol, we found inconsistent administration of a stress-dose of corticosteroids. Only 8% of patients received hydrocortisone according to protocol (chapter 5).(10) In a retrospective study investigating potential postoperative symptoms associated with tertiary adrenal insufficiency, we found no difference in the incidence of postoperative symptoms in the first three postoperative days (chapter 6).(11) However, in a subsequent prospective observational study we observed a potential effect of a stress-dose on the quality of recovery (chapter 7).(12) Further research is necessary to investigate the effect of a stress-dose on postoperative quality of recovery in patients at risk of a tertiary adrenal insufficiency, where residual bias can be adequately controlled for.

Until recently, another guideline recommendation for perioperative administration of corticosteroids was the prevention of postoperative pulmonary complications in patients with chronic pulmonary disease. We found that administration of corticosteroids was also low in this study population (chapter 8).(10,13) Although no new randomized trials had been conducted on this topic, a recent consensus guideline has been developed, reflecting current expert opinion and integrating the latest available evidence.

In this thesis, we found multiple knowledge gaps in perioperative medicine, where the available evidence is limited, which may influence clinical decision making. In this final chapter, the implementation of perioperative protocols and adherence to them are discussed. Next, the challenges in conducting perioperative research will be discussed, as well as the interpretation and applicability of the evidence reported in this

thesis, followed by limitations caused by the infrastructure, and finally implications for future research and clinical practice.

Implementation and Adherence of Perioperative Protocols

Despite the availability of clinical guidelines, adherence to guidelines in the perioperative setting has been shown to be poor. Chapter 5 shows that adherence to guidelines for corticosteroid supplementation is poor, because clinicians do not believe the guideline is evidence based.(10,13) Non-adherence may reflect individual decision-making, but may also be structural, arising from organizational barriers such as unclear responsibilities, workflow constraints, or lack of institutional support.

When introducing a new or updated guideline, the focus should not be limited to the potential clinical benefits. Evidence alone does not necessarily lead to evidence-based practice. Human and organizational factors that influence protocol adherence should also be considered. For example, we observed that documentation of a recommendation to administer stress-dose glucocorticoids at the preoperative assessment clinic appeared to influence whether such therapy was subsequently administered in the perioperative period (unpublished data). In addition, practical considerations seemed to affect protocol adherence. Administration of a single dose of dexamethasone or prednisolone is logistically simpler than hydrocortisone, which requires preparation of a continuous infusion system in addition to an initial bolus dose (chapter 5).(10) The same was observed in the administration of corticosteroids in patients with chronic pulmonary disease, where patients were more likely to receive glucocorticoids if this was advised at the preoperative assessment clinic (chapter 8).(13)

However, once a practice has become part of routine care, it can be equally difficult to de-implement, even when evidence falls short. This phenomenon is known as the implementation paradox or evidence–practice paradox.(14) The paradox may be more common in complex clinical contexts like perioperative care, where multiple disciplines have overlapping responsibility. This might be the case in tertiary adrenal insufficiency, where, despite the absence of compelling evidence, administration of a stress-dose of glucocorticoids is recommended in international guidelines.(10) Given this context, further investigation is challenging, as deviation from established protocols may be perceived as ethically problematic. Similarly, during the conduct of our trial evaluating renin–angiotensin system inhibitors (RASi), we encountered resistance

based on concerns that both continuation and temporary discontinuation might lead to adverse outcomes, despite a lack of evidence supporting either position.(3)

This thesis examined reasons for non-adherence to specific perioperative protocols. The findings reinforce a broader principle: protocols require high-quality evidence before change is initiated, but successful implementation depends on the education of the doctor on this evidence, as well as integration into existing workflow. Furthermore, implementation of new practices takes time, particularly when high-quality evidence is lacking. In summary, successful implementation depends not only on the strength of the evidence but also on human behavior, institutional culture, and practical feasibility.

Challenges in Conducting Research

Conducting clinical research in the perioperative phase poses significant logistical, organizational, and methodological challenges. Answering key questions in perioperative medicine requires collaboration between multiple disciplines, including anesthesiologists, internists, surgeons, and nurses. Patient recruitment may be slow, protocol adherence must be maintained across multiple disciplines and sites, and study interventions need to be implemented consistently. Such structural complexity can impede study coordination, limit recruitment, and reduce the feasibility of adequately powered clinical trials, sometimes leading to early termination.

These challenges were exemplified in our multicenter randomized trial evaluating the perioperative continuation versus temporary discontinuation of RASi (chapter 3). Despite targeting a common patient population and employing a pragmatic study design, only 318 of 2,613 eligible patients (12%) were randomized over 2.5 years across six centers. Recruitment was hampered by COVID-19–related reductions in surgical volume, personnel shortages, and short-term planning at participating hospitals. Furthermore, the observed incidence of acute kidney injury was lower than anticipated, highlighting the challenge of powering perioperative trials to detect clinically relevant differences. We suspect this was caused by the healthy participant effect, in which healthier patients are more likely to participate in a trial, as well as changes over the years in blood pressure regulation and less invasive surgical procedures.(15)

This experience underscores the importance of considering alternative trial designs in perioperative research. Approaches such as cluster randomization or practice-preference randomized consent may improve feasibility by simplifying logistics and increasing patient enrollment. Collectively, these findings illustrate that even straightforward interventions, such as continuing or discontinuing RASi therapy, can face substantial barriers to execution in the perioperative setting and reinforce the need for adaptive and pragmatic strategies in trial design (chapter 3).(3)

Another challenge stems from the inherent nature of many perioperative outcomes. Many clinically important adverse events such as severe perioperative complications are rare, making it difficult to perform sufficiently powered trials. Such a study would involve a large number of patients and is often costly to perform, but does not guarantee a clear answer to the research question. For example, the study might need an inferiority trial as a follow-up, costing more money and requiring more patients to be exposed to study procedures. In these situations, researchers need to carefully balance feasibility, ethical concerns, as well as clinical relevance. Definitive evidence may not always be achievable.

When designing a trial, it must be considered that multicenter trials, which are often necessary to reach a sufficient sample size and produce more generalizable results, come with their own set of challenges. Differences in local workflow, staffing, resources, and regulatory requirements, particularly across countries, add extra complexity. Standardizing protocols and data collection across multiple sites can be time-consuming, and may also limit the flexibility needed to adapt studies to the local clinical practice.(16,17) With regard to patient-reported outcomes, we experienced in chapters 3 and 7 that some patients required extra help with filling out online questionnaires. This proved burdensome for some patients, particularly elderly or frail individuals. These patients often required personal support rather than reliance on digital tools alone.(3,12)

Limited research infrastructure further limits possibilities in perioperative research. In our AIPOP trial, we found that not all participating centers had dedicated study coordinators, which had a substantial impact on patient inclusion and protocol adherence. Additionally, some anesthesiologists in other hospitals were reluctant to perform interventions outside the operating room. This example underscores the

point made in the previous paragraph that research must be supported and conducted collaboratively across multiple disciplines (chapter 3). Competing clinical duties often made it difficult to collect data on time and follow standard operating procedures exactly. These experiences show that successful research relies not only on a solid study design, but also on clear communication, adaptability of both protocol and staff, and active engagement is necessary.(18) A dedicated study coordinator can help to identify these issues early and adapt the study protocol where possible. Smaller hospitals or departments without a dedicated research infrastructure, may be unable to participate. This can reduce the diversity of the study population and may influence the generalizability of the study results to the real-world population undergoing surgery.

Financial and institutional factors also contribute to determining which research projects are feasible. Perioperative medicine tends to receive relatively limited funding, especially when compared with specialties that care for patients with specific diseases in whom medications or interventions are used as first-line therapy. This makes it less attractive for industry-sponsored or commercially driven research. Once funding is secured, studies are often bound by predefined outcomes and strict protocols, making it difficult to modify the study design or include additional outcomes in response to emerging questions. These constraints can result in simpler study designs, shorter follow-up periods, or reliance on surrogate endpoints, choices that make studies more feasible but can limit their relevance to real-world clinical care.(19–21)

Even after overcoming the abovementioned challenges and completing a study, publication may not always be straightforward. Negative or neutral research is also less likely to be published or may only be published in an abbreviated form.(22,23) This selective visibility can contribute to publication bias and mislead doctors reading the results about the strength of the evidence. This could also mislead meta-analyses and guidelines that rely on a pool of evidence. All studies that are well designed and in which the execution and statistical analysis are methodologically sound should be published regardless of the (negative) result. Published studies with negative findings are essential for accurately weighting risks and benefits, possibly avoiding unnecessary interventions.

These challenges show that perioperative research is influenced not only by scientific uncertainty, but also by organizational, financial, and systemic factors. Understanding these limitations is crucial for designing

future studies and for interpreting results realistically within the context of everyday clinical practice.

Electronic Patient Records and Research

Research is a time-consuming and often unpredictable process, requiring careful thought from the very first step of formulating a research question to the final execution of the study. In clinical settings, this process is frequently complicated by the fact that electronic patient records (EPRs) are designed primarily for providing patient care rather than conducting research. Key information needed to identify eligible patients, to track outcomes, or to adjust for important variables is often unstructured, incomplete, or recorded inconsistently. In this thesis, for example, the research questions focused on perioperative medication use, and identifying eligible patients within the EPR often required meticulous manual extraction of data from multiple sources (chapters 3, 5, 6 and 7). This process is not only labor-intensive but also prone to human error, and it can be particularly challenging when multiple hospitals or departments are involved, each with different documentation practices or different EPR systems.

Perioperative research adds further complexity in this regard. Studies must be carefully timed around surgery, interventions often need to be delivered immediately before or after the operation, and follow-up depends on recovery patterns that can vary widely between patients and type of surgical procedure. Accurately recording surgery dates, keeping track of randomization assignments, and ensuring interventions are applied consistently all require close coordination and often rely on manual processes. Engaging patients in the perioperative period is another challenge: before any approach, researchers must verify that patients have consented to be contacted for research, understand the study information, and obtain written consent, all within a short and often stressful time window before surgery.

Several studies included in this thesis required follow-up data, such as laboratory results, questionnaires, and data on complications and hospital readmissions. As the timing of these outcomes was not always clearly documented, data collection often involved repeated and thorough review of medical records, followed by manual data extraction, typically performed by PhD candidates or research students. This manual work may impede patient recruitment and may lead to variable protocol adherence between centers. From our experience in the AIPOP trial,

even seemingly straightforward interventions can become difficult to implement in practice. While not all aspects of research can be automated, there are clear opportunities to improve efficiency in both research and clinical practice. Establishing an interface between research platforms and medical data systems would substantially enhance the efficiency and feasibility of the research process. Automated patient screening, more structured and standardized data capture, electronic consent workflows, and better integration of research processes into clinical systems could dramatically reduce the burden of manual work, decrease errors, and make large-scale perioperative studies more feasible. Investing in research-oriented infrastructure is not just a technical improvement, it directly impacts the ability to answer important clinical questions and improve patient care.

At the same time, these challenges point to opportunities for improvement.

Interpretation and Applicability of Evidence

Interpreting evidence in perioperative medicine is inherently challenging. Many studies are conducted in academic hospitals, which often differ in patient populations, resources, and care processes from smaller or non-academic centers. While these centers often treat patients with multiple comorbidities, study eligibility criteria frequently select for the relatively healthiest among them, as patients with higher risk or more severe conditions are excluded from participation. While this approach improves feasibility and internal validity, it limits the applicability of findings to the more complex patients with multiple comorbidities, who make up the majority of those seen in everyday perioperative practice. (24) Furthermore, outcomes may also be influenced by these selection criteria, such as a lower incidence of acute kidney injury in the AIPOP trial (chapter 3).

In recent years, there has been increasing attention for patient-reported outcomes (PROs) and measures of functional recovery, rather than traditional “hard” endpoints such as complication rates or length of hospital stay.(25) Using patient reported outcomes may enhance the interpretation and applicability of study findings. These outcomes reflect what matters most to patients, including independence, quality of life, and overall wellbeing. However, incorporating PROs into perioperative medication research introduces new challenges. Outcomes can be influenced by multiple factors beyond the intervention itself, such as

baseline health, social context, mental health, and patient expectations.(26,27) They also typically require longer follow-up, which increases study complexity and costs.(28) For future research on perioperative medications, these considerations have several implications. Study designs may need to include more individualized approaches, focusing on changes within patients rather than just group-level comparisons, to capture meaningful improvements in recovery.(29) Integrating PROs also calls for careful planning of follow-up schedules, standardized measurement tools, and strategies to minimize missing data. Ultimately, prioritizing patient-centered outcomes could provide a more comprehensive understanding of how medications influence recovery, helping clinicians tailor perioperative care to what matters most to patients.

CONCLUSION

A persistent knowledge gap, limited evidence, and variability in standard clinical practice mean that perioperative physicians often have to make decisions based on expert opinion, subjective risk–benefit considerations, and individual patient factors. This thesis illustrates that advancing perioperative medicine requires more than high-quality data alone. Across the studies presented in this thesis, we found that even well-designed trials or clinical protocols may fail if they do not account for human behavior, workflow constraints, or the availability of research support.

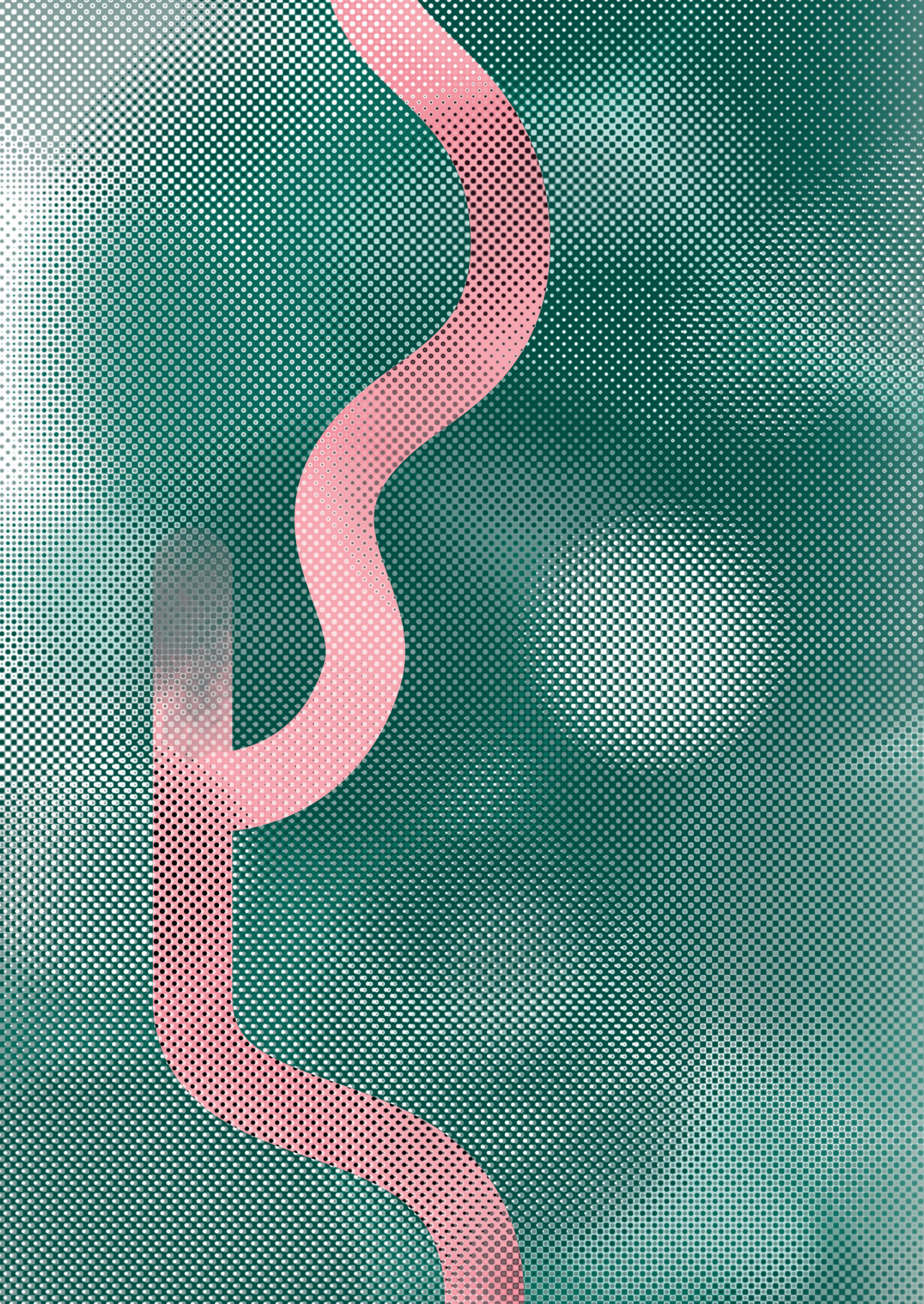
The experiences show that perioperative research and implementation of protocols must consider the realities of clinical practice, including workload, patient characteristics, and available infrastructure. When further research is difficult or outcomes are rare, consensus-based guidance may be the most pragmatic approach, as illustrated by updated recommendations for the prevention of postoperative pulmonary complications. By explicitly reflecting on both evidence and context, this thesis demonstrates that improving perioperative care relies on integrating robust data with practical, patient-centered, and organizational considerations.

REFERENCES

1. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z DP. Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery. Anesthesiology. 2017;(1):16–27.
2. Vassallo MC, Tartamella F, Testa F. Should we withhold angiotensin converting enzyme inhibitors before anaesthesia? An updated debate on the pros and cons. J Clin Anesth. 2017;42:51–2. doi:10.1016/j.jclinane.2017.07.008
3. Miggelbrink LA, van Klei WA, Verhaar MC, Asselbergs FW, Spiering W, Buhre WFFA, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the perioperative period: withdraw or continue? A multicentre randomised controlled trial. Br J Anaesth. 2025 Oct;135(4):1075–7. doi:10.1016/j.bja.2025.05.056
4. Whittle J, Yamal JM, Williamson JD, Ford CE, Probstfield JL, Beard BL, et al. Clinical and demographic correlates of medication and visit adherence in a large randomized controlled trial. BMC Health Serv Res. 2016 Dec 8;16(1):236. doi:10.1186/s12913-016-1471-x
5. Sutton S, Kinmonth AL, Hardeman W, Hughes D, Boase S, Prevost AT, et al. Does Electronic Monitoring Influence Adherence to Medication? Randomized Controlled Trial of Measurement Reactivity. Annals of Behavioral Medicine. 2014 Dec 27;48(3):293–9. doi:10.1007/s12160-014-9595-x
6. Glasgow RE, Knoepke CE, Magid D, Grunwald GK, Glorioso TJ, Waughtal J, et al. The NUDGE trial pragmatic trial to enhance cardiovascular medication adherence: study protocol for a randomized controlled trial. Trials. 2021 Dec 11;22(1):528. doi:10.1186/s13063-021-05453-9
7. Lamberts S, Bruining H, de Jong F. Corticosteroid Therapy in Severe Ilness. New England Journal of Medicine. 1997;337(18):1285–92. PubMed PMID: 12765170.
8. Seo KH. Perioperative glucocorticoid management based on current evidence. Anesth Pain Med (Seoul). 2021;16(1):8–15. doi:10.17085/apm.20089
9. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – A systematic review. Dan Med J. 2018;65(6):1–5. PubMed PMID: 29886882.
10. Miggelbrink LA, Marsman M, van de Wetering J, van Klei WA, Kappen TH. Perioperative corticosteroid supplementation guideline adherence. Anaesthesia. 2025 Jan 30. doi:10.1111/anae.16556
11. Miggelbrink LA, Vroom HB, de Keyser CE, Kappen TH, van Klei WA, van Waes JAR. Effects of a supra-physiological corticosteroid regime in surgical patients at risk for tertiary adrenal insufficiency, a retrospective cohort study. Forthcoming.
12. Miggelbrink LA, Kappen TH, van Oorschot RWH, de Keyser CE, van Klei WA, van Waes JAR. Efficacy of perioperative corticosteroid supplementation in surgical patients at risk of tertiary adrenal gland insufficiency on quality of recovery, an observational cohort study. Not yet published.
13. Miggelbrink L, Marsman M, Senff JR, van Waes JAR, Bronsveld I, van Klei W, et al. Dutch guideline to prevent perioperative pulmonal complications: how is the adherence? Ned Tijdschr Geneeskd. 2022 Oct 20;166. PubMed PMID: 36300494.

14. Owolabi MO, Suwanwela NC, Yaria J. Barriers to implementation of evidence into clinical practice in low-resource settings. Nat Rev Neurol. 2022 Aug;18(8):451–2. doi:10.1038/s41582-022-00690-1 PubMed PMID: 35768655.
15. The healthy participant effect . . . and other stories. BMJ. 2024;386:q1580. doi:10.1136/bmj.q1580
16. van Hout D, Mouncey P, Harrison D, Bonten M, Derde L, Angus DC, et al. Hurdles for the Delivery of Multinational Randomized Clinical Trials. JAMA Netw Open. 2025 Jul 2;8(7):e2518503. doi:10.1001/jamanetworkopen.2025.18503
17. Chung KC, Malay S, Shauver MJ. The Complexity of Conducting a Multicenter Clinical Trial: Taking It to the Next Level Stipulated by the Federal Agencies. Plast Reconstr Surg. 2019 Dec;144(6):1095e–103e. doi:10.1097/PRS.0000000000006271
18. Mello MM, Clarridge BR, Studdert DM. Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry. New England Journal of Medicine. 2005 May 26;352(21):2202–10. doi:10.1056/NEJMsa044115
19. Flight L, Brennan A, Chick SE, Forster M, Julious S, Tharmanathan P. Value-adaptive clinical trial designs for efficient delivery of publicly funded trials - a discussion of methods, case studies, opportunities and challenges. BMC Med Res Methodol. 2025 Jun 5;25(1):153. doi:10.1186/s12874-025-02566-6
20. Greene SJ, Mentz RJ, Fiuzat M, Butler J, Solomon SD, Ambrosy AP, et al. Reassessing the Role of Surrogate End Points in Drug Development for Heart Failure. Circulation. 2018 Sep 4;138(10):1039–53. doi:10.1161/CIRCULATIONAHA.118.034668 PubMed PMID: 30354535.
21. Beca JM, Chan KKW, Naimark DMJ, Pechlivanoglou P. Impact of limited sample size and follow-up on single event survival extrapolation for health technology assessment: a simulation study. BMC Med Res Methodol. 2021 Dec 18;21(1):282. doi:10.1186/s12874-021-01468-7
22. van Lent M, Overbeke J, Out HJ. Recommendations for a uniform assessment of publication bias related to funding source. BMC Med Res Methodol. 2013 Dec 30;13(1):120. doi:10.1186/1471-2288-13-120
23. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database of Systematic Reviews. 2009 Jan 21;2024(12). doi:10.1002/14651858.MR000006.pub3
24. Neville A, Lee L, Antonescu I, Mayo NE, Vassiliou MC, Fried GM, et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. British Journal of Surgery. 2014 Jan 27;101(3):159–70. doi:10.1002/bjs.9324
25. Alam R, Figueiredo SM, Balvardi S, Nauche B, Landry T, Lee L, et al. Development of a patient-reported outcome measure of recovery after abdominal surgery: a hypothesized conceptual framework. Surg Endosc. 2018 Dec 17;32(12):4874–85. doi:10.1007/s00464-018-6242-9
26. Kawai T, Kataoka M, Goto K, Kuroda Y, So K, Matsuda S. Patient- and Surgery-Related Factors that Affect Patient-Reported Outcomes after Total Hip Arthroplasty. J Clin Med. 2018 Oct 15;7(10):358. doi:10.3390/jcm7100358
27. Nkemdirim Okere A, Moussa RK, Ali AA, Li T, Buxbaum SG, Diaby V. Patient-reported outcomes and perceived medication confidence as predictors of healthcare utilization among adults with cardiovascular risk factors. Sci Rep. 2025 Dec 5. doi:10.1038/s41598-025-31255-z

28. Klaic M, Kapp S, Hudson P, Chapman W, Denehy L, Story D, et al. Implementability of healthcare interventions: an overview of reviews and development of a conceptual framework. Implementation Science. 2022 Dec 27;17(1):10. doi:10.1186/s13012-021-01171-7
29. Caruana EJ, Roman M, Hernández-Sánchez J, Solli P. Longitudinal studies. J Thorac Dis. 2015 Nov;7(11):E537-40. doi:10.3978/j.issn.2072-1439.2015.10.63 PubMed PMID: 26716051.



PART IV
ADDENDUM



CHAPTER 10

General summary
Nederlandse samenvatting

GENERAL SUMMARY

Annually, over 200 million people undergo non-cardiac surgery worldwide. Although non-cardiac surgery is generally safe, today's surgical population is older, has multiple comorbidities and polypharmacy is common. The use of chronic medications may (unexpectedly) influence postoperative outcomes. However, for many commonly used drugs, it is not truly known which policy is best around surgery: supplementation or not, to continuation or discontinuation, and if so, for how long. This thesis comes forth out of that uncertainty. Its purpose was to better understand how perioperative management of chronic medications may influence postoperative recovery and complications.

Part I of this dissertation examines a long-standing clinical dilemma: should patients on angiotensin-converting-enzyme inhibitors or angiotensin-II receptor blockers continue these drugs in the perioperative phase, or should they be discontinued? Continuing them may maintain cardiovascular stability, whilst withholding may reduce the risk of intraoperative hypotension and postoperative acute kidney injury (AKI). For years, there was no definitive evidence to guide clinicians, and international guidelines differed from one another. This uncertainty led to the development of the AIPOP trial, a randomized study designed to compare continuation versus discontinuation of angiotensin-inhibiting drugs in a broad non-cardiac surgical population. The study protocol is described in **Chapter 2**, laying out the design that aimed to answer this clinical question systematically. Unfortunately, recruitment challenges resulted in early termination of the study. The results and lessons learned from this trial are presented in **Chapter 3**. We found no difference in the incidence of postoperative AKI between the continuation and discontinuation groups. However, because the early termination left the study underpowered, the findings cannot conclusively rule out a clinically meaningful difference. Instead, they highlight the difficulty of large-scale perioperative medication trials, and the enduring importance of collaborative multicenter efforts. In **Chapter 4** we investigated adherence to medication instructions (continuation or discontinuation of angiotensin inhibitors) before surgery by patients in the AIPOP trial through measurements of medication levels in blood. Based on these measurements, half of patients seemed not to have followed the instructions, especially in the group of patients who received instructions to discontinue this medication. In light of the results of recent trials that showed no benefit of discontinuation over continuation of angiotensin

inhibitors, it seems most appropriate to advise patients to continue their antihypertensive medications before surgery.

In Part II we studied the effect of glucocorticoid supplementation in patients around surgery. We began by studying surgical patients on chronic corticosteroid therapy, who therefore are at risk of tertiary adrenal insufficiency. Because their adrenal gland function may be suppressed, the normal physiologic stress response to surgery may be blunted. To prevent adrenal insufficiency, guidelines recommend giving these patients a perioperative stress-dose of corticosteroids, but in clinical practice this recommendation is not always followed. In **Chapter 5** we found that only 8% of at-risk patients received corticosteroids according to protocol, while nearly half (48%) received corticosteroids for other clinical indications. In **Chapter 6**, we retrospectively examined whether treatment with corticosteroids affected postoperative symptoms possibly related to adrenal insufficiency. Compared with control patients, patients with an indication for a corticosteroid stress-dose given either an adequate stress dose or a lower corticosteroid dose, did not report an increase in postoperative symptoms during the first three days. However, as this was a retrospective study, symptoms may have been underreported, and subtle endocrine dysregulation may not always be captured in routine documentation. To strengthen the evidence, we turned to a prospective approach. In **Chapter 7**, we performed a prospective observational cohort study to assess postoperative quality of recovery in patients at risk for tertiary adrenal insufficiency and in control patients. An adjusted analysis showed that patients who did not receive a corticosteroid stress-dose may have impaired postoperative recovery as compared to patients who did receive such supplementation. We found no effect of glucocorticoids on recovery in the control group. This study suggests that stress-dose steroids *may* help preserve quality of recovery, a hypothesis that warrants a large, randomized trial.

Chapter 8 explored a different rationale for perioperative corticosteroid administration: prevention of pulmonary complications in patients with asthma or COPD undergoing surgery. We found that guideline adherence was only moderately successful. Anesthesiologists were more likely to administer corticosteroids in patients with more severe pulmonary disease, but overall variability remained high. Interviews and practice pattern analysis revealed several barriers: insufficient patient-specific detail in the guideline, limited supporting evidence in cases involving

loco-regional anesthesia, and notable differences in how pulmonologists and anesthesiologists interpret the same recommendations.

In summary, this dissertation tells a larger story: perioperative management of chronic medication is a critical but under-studied pillar of perioperative care. Whether the question is (dis)continuing antihypertensives, supplementing corticosteroids, or aligning specialists on guidelines to prevent postoperative pulmonary complications, the evidence gaps remain substantial. The studies in this thesis do not provide all the answers, but they illuminate where the uncertainties lie, where practice varies, and where future research should be directed. Ultimately, the goal remains clear: to enable safer surgery and smoother recovery for the growing population of multimorbid, medicated patients who entrust us with their care.

DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Jaarlijks ondergaan wereldwijd meer dan 200 miljoen mensen een niet-cardiale operatie. Hoewel niet-cardiale chirurgie over het algemeen veilig is, is de huidige chirurgische populatie ouder, hebben zij meerdere comorbiditeiten en komt polyfarmacie veel voor. Het gebruik van chronische medicatie kan (onverwacht) invloed hebben op postoperatieve uitkomsten. Voor veelgebruikte geneesmiddelen is echter niet duidelijk wat het beste beleid rondom een operatie is: suppleren of niet suppleren, continueren of staken, en zo ja, voor hoe lang. Dit proefschrift is voortgekomen uit deze onzekerheid. Het doel was om beter te begrijpen hoe perioperatief beleid ten aanzien van chronische medicatie het postoperatieve herstel en complicaties kan beïnvloeden.

Deel I van dit proefschrift onderzocht een al lang bestaand klinisch dilemma: moeten patiënten die angiotensineremmers zoals angiotensin-converting enzyme (ACE)-remmers of angiotensine-II receptorblokkers (ARB's) gebruiken deze medicatie in de perioperatieve fase continueren, of juist staken? Het continueren kan bijdragen aan hemodynamische stabiliteit, terwijl staken mogelijk het risico op intraoperatieve hypotensie en postoperatief acuut nierfalen (AKI) vermindert. Jarenlang ontbrak overtuigend bewijs om clinici te ondersteunen, en internationale richtlijnen verschilden van elkaar. Deze onzekerheid vormde de aanleiding van de AIPOP-studie, een gerandomiseerde studie waarin continueren versus staken van angiotensineremmers werd onderzoek bij patiënten die niet-cardiale chirurgie ondergingen. Het studieprotocol wordt beschreven in **Hoofdstuk 2** en schetst het ontwerp dat deze klinische vraag systematisch moest beantwoorden. Helaas leidde moeizame inclusie tot vroegtijdige beëindiging van de studie. De resultaten en lessen worden gepresenteerd in **Hoofdstuk 3**. We vonden geen verschil in de incidentie van postoperatief acuut nierfalen tussen de groepen. Door de vroegtijdige beëindiging had de studie onvoldoende "statistische power", waardoor een klinisch relevant verschil niet kan worden uitgesloten. De resultaten benadrukken de moeilijkheid van grootschalige perioperatieve medicatiestudies en het belang van multicenter samenwerking. In **Hoofdstuk 4** onderzochten we therapietrouw van patiënten aan de instructies (continueren of staken van angiotensineremmers) vóór de operatie door medicatiespiegels in het bloed te meten. Hieruit bleek dat ongeveer de helft van de patiënten de instructies niet had gevolgd, met name in de groep die moest stoppen. In

het licht van recente studies die geen voordeel tonen van staken boven continueren van angiotensineremmers, lijkt het het meest passend om patiënten te adviseren hun antihypertensieve medicatie vóór de operatie te blijven gebruiken.

In Deel II onderzochten we het effect van glucocorticoïd suppletie rondom operaties. We begonnen met patiënten die chronisch corticosteroïden gebruiken en daardoor risico lopen op een tertiaire bijnierinsufficiëntie. Omdat hun bijnierfunctie onderdrukt kan zijn, kan de normale fysiologische stressrespons op chirurgie verstoord zijn. Om dit te voorkomen, adviseren richtlijnen perioperatieve toediening van een stressdosis corticosteroïden, maar in de praktijk wordt dit niet altijd opgevolgd. In **Hoofdstuk 5** vonden we dat slechts 8% van de risicopatiënten corticosteroïden volgens protocol kreeg, terwijl bijna de helft (48%) corticosteroïden ontving voor andere indicaties. In **Hoofdstuk 6** onderzochten we retrospectief of behandeling met corticosteroïden invloed had op postoperatieve symptomen die mogelijk samenhingen met een (tertiaire) bijnierinsufficiëntie. Patiënten met een indicatie voor een stressdosis rapporteerden, ongeacht of zij een adequate of lagere dosis kregen, geen toename in postoperatieve symptomen gedurende de eerste drie dagen. Omdat dit een retrospectieve studie was, kunnen symptomen onder gerapporteerd zijn en subtiele endocriene ontregelingen gemist zijn. Daarom volgde een prospectief onderzoek. In **Hoofdstuk 7** voerden we een prospectieve observationele cohortstudie uit naar de kwaliteit van herstel bij risicopatiënten en controle patiënten. Na correctie bleek dat patiënten die geen stressdosis corticosteroïden kregen, mogelijk een slechter postoperatief herstel hadden dan patiënten die wel suppletie hadden ontvangen. In de controlegroep werd geen effect van glucocorticoïden gevonden. Deze studie suggereert dat stressdoses het herstel kunnen ondersteunen, een hypothese die nader onderzocht moet worden in een grote gerandomiseerde studie.

Hoofdstuk 8 verkende een andere reden voor perioperatieve corticosteroïdtoediening: het voorkomen van pulmonale complicaties bij patiënten met astma of COPD die een operatie ondergaan. We vonden dat de opvolging van de richtlijn matig was. Anesthesiologen dienden vaker corticosteroïden toe bij patiënten met ernstigere longaandoeningen, maar de variatie in de praktijk bleef groot. Interviews en analyse van praktijkpatronen toonden verschillende barrières: onvoldoende patiënt specifieke details in richtlijnen, beperkte evidentie bij locoregionale anesthesie, en

verschillen in interpretatie van richtlijnen tussen longartsen en anesthesiologen.

Samenvattend vertelt dit proefschrift een breder verhaal: perioperatief beleid rondom chronische medicatie is een cruciale maar onderbelichte pijler van de perioperatieve zorg. Of het nu gaat om het (niet) continueren van antihypertensiva, het suppleren van corticosteroïden, of het afstemmen van richtlijnen tussen specialisten om pulmonale complicaties te voorkomen, de kennislacunes blijven groot. De studies in dit proefschrift geven niet alle antwoorden, maar maken duidelijk waar de onzekerheden liggen, waar de praktijk varieert en waar toekomstig onderzoek zich op moet richten. Het uiteindelijke doel blijft helder: veiligere chirurgie en een beter herstel mogelijk maken voor de groeiende populatie van multimorbide patiënten met polyfarmacie, die hun zorg aan ons toevertrouwen.

ACKNOWLEDGEMENTS | DANKWOORD

Direct uit de schoolbanken ben ik ooit begonnen met een combinatie als arts-assistent niet in opleiding op de preoperatieve screeningpoli in combinatie met een opleidingstraject. Dit was in 2018... Inmiddels zijn we een hele periode verder, waarin ik naast mijn promotie, ook mijn opleiding tot anesthesioloog heb afgemaakt.

Ik ben dankbaar voor de begeleiding van een promotieteam, dat mijns inziens niet beter had kunnen zijn. Jullie betrokkenheid, expertise en persoonlijke steun maakten dit traject bijzonder waardevol voor mij. Professor van Klei, beste **Wilton**, dank voor de kans en je scherpe, snelle feedback. Je combineert duidelijkheid met flexibiliteit op een inspirerende wijze. Dankzij jou kon ik mijn ideeën beter verwoorden. Waar ik een hele alinea nodig had, kon jij het herschrijven tot één duidelijke zin. Ik hoop ooit zelf promovendi te begeleiden, waarin ik jouw stijl ter harte neem! Dr. van Waes, **Judith**, bedankt voor je wijze lessen, zowel wetenschappelijk als in de rol van (destijds toekomstig) anesthesioloog. Je liet me het belang van balans tussen kliniek en onderzoek zien. Ook vond ik je begeleiding en mentorschap rondom het stopzetten van de AIPOP-trial zeer prettig. Dr. Kappen, **Teus**, ik heb je betrokkenheid als copromotor enorm gewaardeerd. Onze gesprekken waren inhoudelijk én persoonlijk verrijkend. Je geduld en uitleg gaven me inzicht in statistiek en een kritische blik op onderzoek. En, hoewel vervloeken een groot woord is, heeft het regelmatige "zetje in de juiste richting" mij wel verder gebracht binnen het doen van onderzoek.

Tijdens mijn opleiding tot anesthesioloog was er veel ruimte om, soms ook enigszins ongepland, mijzelf weer in het onderzoek te gooien. Professor Hoff, **Reinier**, je bent mijn enige opponent die ook een (officiële) rol heeft gehad binnen mijn opleiding. Je gaf mij de kans om onderzoek te combineren met mijn opleiding tot anesthesioloog, wat ik als enorm waardevol heb ervaren. Je dacht actief mee over mogelijkheden, gaf ruimte voor eigen invulling en bood ondersteuning, ook door het inzetten van competentietijd. Die flexibiliteit was waardevol, al bracht het ook uitdagingen met zich mee. **Gersten**, van proefpersoon in jouw studie tot AIOS onder jouw begeleiding, en nu zelfs collega anesthesioloog — een bijzondere ontwikkeling. Ondanks dat mijn promotie al ver gevorderd was toen jij deze rol overnam, hebben we samen zorgvuldig gekeken naar de balans tussen opleiding en PhD. Je begrip en steun voor mijn al ingeslagen pad hebben veel betekend. **Myra**, je kreeg pas later in mijn

gehele traject van PhD en AIOS een rol, maar bedankt voor de steun in deze laatste fase!

Een promotietraject doorloop je nooit alleen – de steun van collega's is onmisbaar, zowel tijdens het onderzoek als op de werkvloer. In het bijzonder op de onderzoekskamer heb ik het voorrecht gehad om samen te werken met een geweldige groep (toekomstige) onderzoekers: **Tessa, Nikki, Katja, Jelle, Matthijs, Eva, Marjelle, Emma, Lisa, Fienke, Britney, en Nena**. Dank jullie wel voor de fijne tijd die we samen hebben doorgebracht, zowel op de onderzoekskamer én tijdens de PhD-uitjes. We hebben lief en leed gedeeld, hoogte- én dieptepunten meegemaakt, en het was ontzettend waardevol om een groep te hebben die precies begrijpt waar je doorheen gaat.

Beste **collega (oud-)AIOS**, dank jullie wel voor het begrip tijdens mijn afwezigheid in de onderzoeksperiodes. Jullie steun, en de momenten waarop we even konden praten (met koffie) of sparren, hebben veel voor me betekend. **Eveline**, jou wil ik in het bijzonder bedanken. Het luisterend oor, mijn studeermaatje, steun en toeverlaat gedurende de stress rondom het beruchte NVA-examen… Ik had dit met niemand anders willen doen! Aan alle **anesthesiologen**: de kliniek heeft voor mij altijd op één gestaan, maar soms moest de OK wijken voor een essentiële afspraken voor mijn onderzoek. Dank voor jullie begrip, jullie steun en het vertrouwen. Ik ben dankbaar voor alles wat ik tot nu toe heb geleerd – en uitkijkend naar alles wat ik nog mag leren tijdens mijn tijd als jong staflid. In het bijzonder wil ik ook **Oscar van den Bosch** bedanken. Ooit begonnen als een "side project", heb ik ook weer veel mogen leren van het onderzoek doen en het schrijven van het artikel met jou samen. Je was (en bent) een mentor buiten mijn promotieteam, enorm waardevol!

Gedurende mijn PhD, ANIOS en AIOS-tijd, heb ik met veel mensen samen mogen werken. Door de steun van iedereen in dit gehele traject, heb ik alles kunnen doen. **Marije**, van ANIOS naar AIOS onder jouw hoede én samenwerking aan artikelen—ik heb veel respect voor hoe jij je promotie, werk als anesthesioloog, hoofd POS en gezin wist te combineren. Met jou als voorbeeld, gaf het mij het vertrouwen dat al deze ballen gelijktijdig in de lucht gehouden konden worden. Aan alle **coauteurs** en iedereen die heeft bijgedragen aan de AIPOP-studie, ontzettend bedankt! Hoewel het besluit om de studie te stoppen niet uit het niets kwam, waardeerde ik het meedenken over de vervolgstappen enorm. De **studenten** die ik tijdens mijn promotie begeleidde, hebben met hun inzet bij de dataverzameling

en andere taken een waardevolle bijdrage geleverd. Ik heb veel van het begeleiden van jullie geleerd.

Tijdens mijn promotietraject werkte ik samen met velen van het **trialbureau en datamanagers**. Jullie inzet bij de uitvoering van de studies en het verkrijgen van benodigde data was onmisbaar. In het bijzonder wil ik **Gea** noemen, die altijd voor me klaarstond, regelmatig ongevraagd taken oppakte en een luisterend oor bood wanneer dat nodig was.

Mijn zeer geliefde en geleerde **paranimfen**, **Nikki en Nora**, wat bijzonder fijn dat jullie mij willen bijstaan tijdens de verdediging van dit proefschrift. Het resultaat van heel wat bloed, zweet en tranen. Jullie aanwezigheid op die spannende dag zal ongetwijfeld helpen om de zenuwen enigszins in toom te houden. Dank jullie wel dat jullie aan mijn zijde staan!

Inspiratie begint vaak vroeg, en voor mij speelde de middelbare school daarin een belangrijke rol. De bevlogenheid en betrokkenheid van mijn leraren hebben bijgedragen aan mijn interesse in wetenschap en onderzoek – iets waar ik hen nog steeds dankbaar voor ben. **Marieke**, jij begon ooit als mijn scheikundelerares, maar onze band is in de loop der jaren uitgegroeid tot een waardevolle vriendschap. Het is bijzonder om te zien hoe onze paden zich zo hebben ontwikkeld. **Michel**, jij gaf mij biologieles als brugpieper, en je enthousiasme voor het vak was aanstekelijk en inspirerend. Je hebt mijn hele opleiding van dichtbij gevolgd, tot en met mijn afstuderen als arts – en nu hoop ik je ook bij mijn promotie te mogen betrekken. “Full circle” zoals ze ook wel zeggen. **Kees**, in mijn laatste drie middelbare schooljaren had ik biologie van jou. Ik had diep respect voor je als docent vanwege je kennis, maar achteraf gezien misschien ook vanwege je achtergrond in onderzoek. Een inspiratie voor types zoals ik…

Hoewel iedereen in het ziekenhuis van onschatbare waarde is, zijn het juist vriendinnen en familie die je helpen om af en toe even los te komen van het promotietraject en je met heel andere dingen bezig te laten zijn. **Inge en Marianne** – we begonnen ooit samen als brugpiepers op de middelbare school, en inmiddels zijn we vele jaren verder als hechte vriendinnen. **Monika**, jij bent inmiddels ook niet meer weg te denken uit onze groep. Jullie hebben me er vaak doorheen gesleept in drukke tijden. Dank jullie wel voor jullie steun, jullie geduld en het begrip voor mijn overvolle agenda. Inge, speciaal dank ook aan jou voor het ontwerpen van het AIPOP-logo én de prachtige cover van dit proefschrift – wat bijzonder

dat jij daar je creativiteit in hebt willen steken! **Sandra**, al samen sinds de geneeskunde opleiding. Bedankt voor de gezelligheid en steun, en dat je soms ook even vroeg hoe dat onderzoek nou ging…

Mijn ouders en mijn zus hebben mij altijd gesteund, ook als dit soms zorgde dat ik op vakanties en weekendjes weg ook even het een en andere moest regelen. Lieve **Xanne**, ook al verschillen we als persoon en in onze carrières behoorlijk, er is juist ook zoveel dat ons verbindt. Tijdens mijn studie hielp jij mij met jouw gevorderde kennis, en inmiddels ben jij ook al even gepromoveerd op een heel indrukwekkend onderwerp – wat een mijlpaal! Nu is het mijn beurt. Ondanks onze verschillende vakgebieden is het altijd fijn om met jou over onderzoek te sparren. Thanks, big sis!

Lieve **pap en mam**, jullie hebben me altijd onvoorwaardelijk gesteund in alles wat ik ondernam. Jullie leerden me doorzetten wanneer het nodig was, en relativeren als het tegenzat. Die levenslessen hebben ervoor gezorgd dat dit promotietraject niet alleen haalbaar, maar ook waardevol en leerzaam is geweest. Dank jullie wel, uit het diepst van mijn hart.

ABOUT THE AUTHOR

Lynn Ann Miggelbrink was born on December 30, 1992, in Geleen, the Netherlands. She completed her secondary education in 2011 at Het IJsselcollege in Capelle aan den IJssel. That same year, she began studying Medicine at Utrecht University, where she obtained her Medical Doctor degree in 2018.

Following her graduation, she worked as a junior doctor in the Department of Anesthesiology at the University Medical Center Utrecht (UMCU). There, she conducted research on perioperative medication under the supervision of Prof. Dr. W.A. van Klei, Dr. J.A.R. van Waes, and Dr. T.H. Kappen. During this time, she also initiated several new research projects and developed multiple research databases.

After conducting a systematic search on the continuation versus withdrawal of angiotensin inhibitors in the perioperative setting, her research team secured funding for a related clinical study. As coordinating investigator, she designed and led the AIPOP study, overseeing its implementation and coordination in multiple hospitals.

In 2021, Lynn started her residency in Anesthesiology at the University Medical Center Utrecht, where she combined clinical training with research activities. In June 2026 she started working as a fellow in pediatric anesthesia in the Wilhelmina Children's hospital, Utrecht. Her long-term ambition is to combine clinical work as an anesthesiologist with an active role in scientific research.

LIST OF PUBLICATIONS

This dissertation

Miggelbrink LA, van Klei WA, Verhaar MC, Asselberg FW, Buhre WFFA, Hollman MW, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the peri-operative period: to withdraw or to continue? A multicentre randomised controlled trial. Br J Anaesth. 2025 Oct;135(4):1075-1077. DOI: 10.1016/j.bja.2025.05.056

Van Waes JAR, **Miggelbrink LA**, van der Elst KCM, Smeijsters EH, van Klei WA. Adherence to medication intake instructions before surgery in patients taking renin-angiotensin system inhibitors. Preprint Br J Anaesth. Br J Anaesth. 2026 Sep 21:S0007-0912(26)00619-7. doi: 10.1016/j.bja.2026.07.052.

Miggelbrink LA, Marsman M, de Wetering J, de Ranitz-Greven WL, van Waes JAR, van Klei WA et al. Peri-operative corticosteroid supplementation guideline adherence. Anaesthesia 2025 Apr;80(4):454-455. DOI: 10.1111/anae.16556

Miggelbrink LA, Marsman M, Senff JR, van Waes JAR, Bronsveld I, van Klei WA, et al. Perioperatieve inhalatie medicatie en toediening van systemische corticosteroïden in patiënten met pulmonale aandoeningen: een retrospectieve studie met gemengde methoden voor naleving van protocol. Ned Tijdschr Geneeskd. 2022;166:D6889. DOI: 10.51770/D6889

Other publications

Miggelbrink LA, Nijman TAJ, Megens JHAM, van den Bosch OFC. Management of accidental pre-incisional administration of carbetocin in Caesarean delivery. Br J Anaesth. 2026 Mar;136(3):1059-1061. DOI: 10.1016/j.bja.2025.12.012

Miggelbrink LA, van Loon K, Lindeboom F, Schaap TP, Buhre WFFA, van den Bosch OFC. Maternal hypotension and efficacy of intrathecal clonidine for cesarean delivery: a retrospective cohort study (2011-2022). Int J Obstet Anesth. 2026 Aug:67:105205. DOI: 10.1016/j.ijoa.2026.105205

