

An abstract painting of a human leg, focusing on the venous system. The leg is depicted with bold, expressive brushstrokes in deep blue, red, and black. A prominent white, lattice-like structure, representing a venous stent, is visible in the center of the leg, extending from the knee down towards the ankle. The overall style is expressive and artistic, with a focus on color and form rather than realistic detail.

Endovenous
Treatment with Stents for
Acute Iliofemoral
Deep Vein Thrombosis and
Post-thrombotic
Syndrome

J.M. (Jay) Bakas

Life after a
Venous Stent

Journal

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Endovenous Treatment with Stents for Acute Iliofemoral Deep Vein Thrombosis and Post-thrombotic Syndrome

Jay M. Bakas

24 Juni 2026 om 15.30 uur.

1. The beginning is the most important part of the work, in terms of venous stent patency.
– This thesis.
2. Inflow disease increases the risk of venous stent patency loss in post-thrombotic syndrome.
– This thesis.
3. Evolution of (lytic-free) thrombectomy devices potentially lowers the threshold for invasive treatment of acute iliofemoral deep vein thrombosis.
– This thesis.
4. Physical functioning should be monitored in post-thrombotic syndrome, even after successful treatment with venous stents.
– This thesis.
5. Mental functioning deserves attention after invasive treatment for acute deep vein thrombosis.
– This thesis.
6. “If you cannot measure it, you cannot improve it.”
– William Thomson, Lord Kelvin, (1824-1907).
7. “Everything should be made as simple as possible, but not simpler.”
– Albert Einstein, (1879-1955).
8. “There is a tool for every task, and a task for every tool.”
– George R.R. Martin (1948 – heden); A Song of Ice and Fire; Tywin Lannister, Game of Thrones.
9. “The most fruitful and natural exercise for our minds is, in my opinion, conversation.”
– Michel de Montaigne (1533 – 1592).
10. “Prevention is better than cure.”
– Desiderius Erasmus (1466 – 1536).
11. “Eens dan wordt de hemel stralend blauw.”
– Thijs van der Molen (1938 – 2019).

**Endovenous Treatment with Stents for Acute
Iliofemoral Deep Vein Thrombosis and
Post-thrombotic Syndrome**

Life after a Venous Stent

Jay Marlon Bakas

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Endovenous Treatment with Stents for Acute Iliofemoral Deep Vein Thrombosis and Post-thrombotic Syndrome

Endoveneuze behandeling met stents voor acute iliofemorale diep veneuze trombose en posttrombotisch syndroom

Proefschrift

ter verkrijging van de graad van doctor aan de
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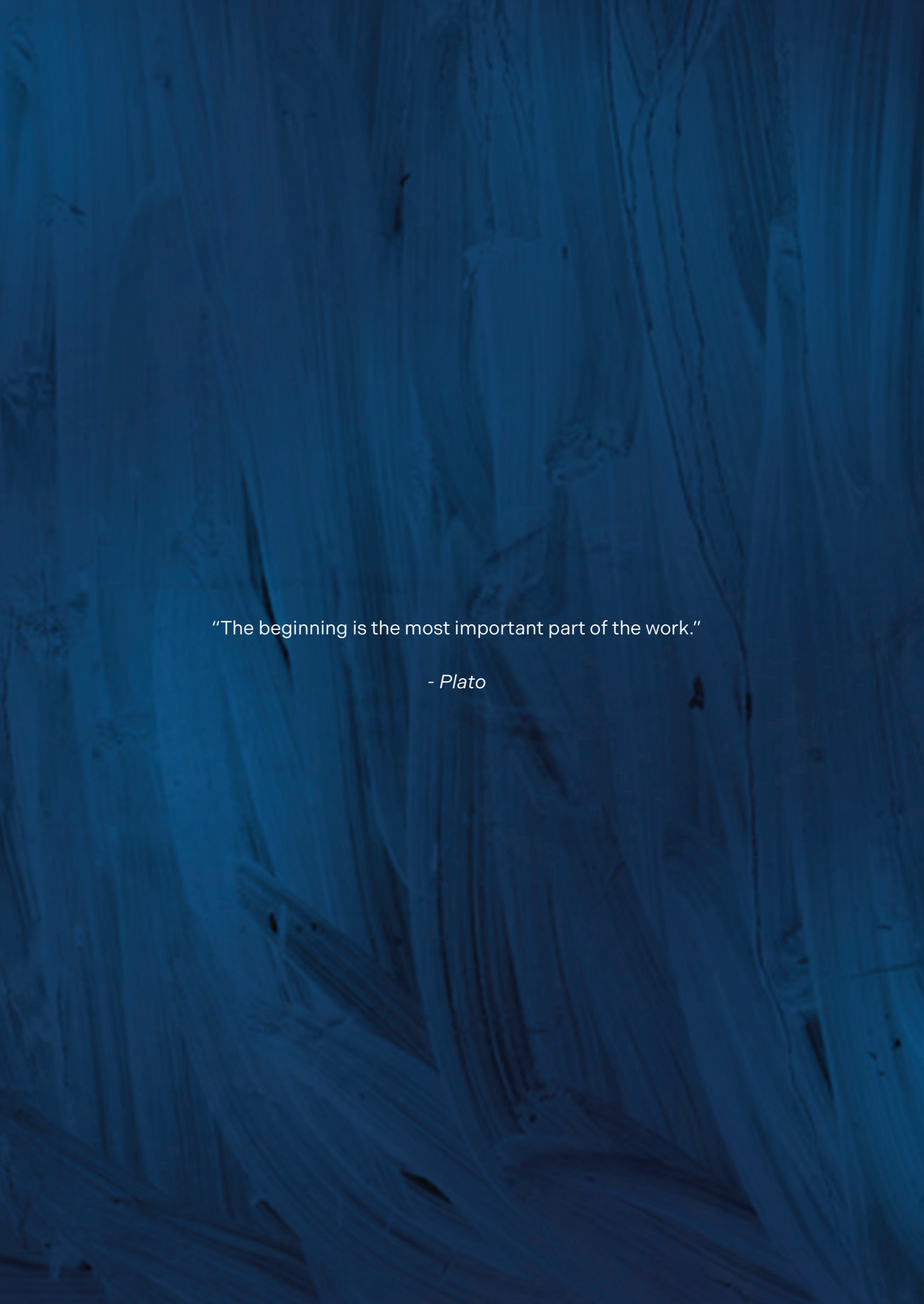
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Dr. G.M. van der Wilden

Copromotoren: Dr. M.J.E. van Tongerlo - van Rijn
Dr. A. Moelker (in memoriam)

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"The beginning is the most important part of the work."

- *Plato*



GENERAL INTRODUCTION

Acute deep vein thrombosis and post-thrombotic syndrome

Deep vein thrombosis (DVT) is a prevalent disease, annually affecting 1-2 out of 1000 patients.¹ Patients with iliofemoral DVT – which affects the iliac vein(s) and/or common femoral vein, with or without extension into the inferior vena cava (IVC) – tend to present with more severe symptoms and signs than patients with femoropopliteal and calf vein DVT.² Deep venous thrombosis may affect the whole lower limb in severe cases of iliofemoral DVT, causing a limb-threatening condition (phlegmasia cerulea dolens).³ An adequate treatment of iliofemoral DVT is required for an immediate relief of symptoms and signs in the acute phase, and possibly to prevent incurable conditions of deep venous insufficiency in the chronic phase, known as post-thrombotic syndrome (PTS). Post-thrombotic syndrome is a severe chronic complication after acute DVT, causing various symptoms and signs, such as by pain, itching, skin changes, edema, and even venous ulceration.⁴ The condition is caused by intraluminal changes such as damaged venous valves, trabeculation, or both, leading to venous obstruction and/or reflux, causing venous hypertension.⁵

Conservative treatment

Non-invasive “conservative” treatment should be considered for all acute DVT patients. Conservative treatment includes oral anticoagulant therapy, compression therapy, and physical exercise. Oral anticoagulant therapy cannot prevent development of intraluminal changes in iliofemoral DVT, due to large volume blood clots.⁶ This possibly explains increased PTS risk in iliofemoral DVT compared with “distal” DVT.⁷ Individualized therapy with elastic compression stockings is an effective method to prevent PTS in acute DVT patients, and potentially enhances patient well-being.⁸ Physical exercise is safe and should be recommended early after acute DVT, since it improves quality of life, reduces pain, and decreases PTS severity.⁹

Quality of life

Quality of life (QoL) is usually comparable with the general population within the first year following acute DVT, but is strongly impaired if PTS develops.¹⁰ The CEAP classification (Clinical, Etiological, Anatomical, Pathophysiological) is an international standard to describe chronic venous disorders (such as PTS) based on the clinical manifestations, currently understood etiology, involved anatomy, and underlying pathology.^{11,12} Various patient-reported outcome measures (PROMs) are available to determine QoL and health functioning levels of PTS patients. The Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) is a validated 20-question disease-specific questionnaire, used to address quality of life in chronic venous disease.¹³ The VEINES-QOL/Sym is another patient-reported questionnaire to evaluate symptoms and QoL in chronic

venous disorders of the leg based on 26 items.¹⁴ A common used validated survey for general health-related QoL, is the 36-item Short Form Health Survey (SF-36), which depicts both mental and physical aspects of general health.¹⁵

Certain PTS patients have a comparable QoL to patients with severe chronic diseases such as chronic obstructive lung disease, diabetes mellitus, and heart failure.¹⁶ Ulceration is the most devastating sign and most expensive complication of PTS, associated with work absence, unemployment, and increased medical costs¹⁷: emphasizing that PTS development should be prevented. Post-thrombotic syndrome develops in 20-50% of iliofemoral DVT patients.^{18,19} These numbers might be underestimated since PTS development takes time – from months to several years – and is often overlooked because of abandoned outpatient clinic follow-up. Current scoring systems for PTS are insufficient. The Villalta scale is a recommended and commonly used PTS scoring tool, which estimates PTS severity during follow-up.^{4,20} Several symptoms such as venous claudication are not included in Villalta, potentially causing underdiagnosis and underestimation of PTS. The population affected by PTS is expected to grow as well, since the incidence of venous thrombotic events have also been increased.²¹ The incidence of PTS might become even higher than expected due to increased DVT rates during the SARS-CoV-2 pandemic.^{22,23}

Endovenous treatment

The introduction of endovenous treatment techniques has changed the medical field for acute DVT and PTS treatment over the past decades. Endovenous treatment brings the opportunity to restore venous patency and resolve symptoms and signs for both acute DVT and PTS.²⁴ Improved QoL outcomes have been reported after successful interventions for venous occlusive disease.^{25,26} Treatment strategies for acute DVT and PTS have been changed, with the introduction of dedicated venous stents, intravascular ultrasound, multidisciplinary teams, and new endovenous techniques for early clot removal. Endovenous procedures should be considered to treat symptomatic iliofemoral outflow obstruction according to European Society for Vascular Surgery (ESVS) guidelines.^{27,28} Endovenous treatment includes pharmacological and/or mechanical thrombectomy devices⁶, and are often followed by implantation of venous stents. The first procedure including treatment with deep venous stents for iliofemoral outflow obstruction was reported in 1995.²⁹ Plenty of cases have been reported since, with venous stent patency outcomes ranging between 59-94% primary patency (= percentage of open stents without re-intervention), and 89-100% secondary patency (= percentage of open stents after re-intervention).³⁰ Long-term patency data after DVT and PTS treatment with deep venous stents are scarce, since patency follow-up is limited to 1 or 2-years in most studies.

Anticoagulation management

Hypercoagulability, blood stasis, and endothelial injury are predisposing factors for acute DVT, known as Virchow's triad.³¹ Anticoagulant therapy is initiated to stop ongoing blood clot formation and prevent recurrent venous thromboembolism (VTE) following acute DVT, but its role in PTS treatment is unknown.³² For anticoagulant therapy, low-molecular weight heparin, vitamin-K-antagonists, or direct-oral anticoagulants are prescribed. Duration of anticoagulant therapy depends on the presence of a DVT "provoking" factor. A DVT is referred to as "provoked" if an underlying cause for venous thromboembolism is present (e.g. immobilization, malignancy, pregnancy) and referred to as "unprovoked" if provoking factors are absent (idiopathic).³³ While cessation of anticoagulant therapy is considered after provoked DVT (if the provoking factor has been resolved), a prolonged or even lifelong anticoagulants treatment is recommended for unprovoked DVT.³⁴ Iliofemoral DVT is frequently associated with left iliac vein compression syndrome (LIVCS) – also known as May-Thurner syndrome – in which the right common iliac artery compresses the underlying left iliac vein.³⁵ Venous stents could resolve mechanical compression in LIVCS, but it still remains controversial whether LIVCS counts as a provoking factor for DVT. Understanding whether (left-sided) iliofemoral DVT is mainly caused by LIVCS or by other factors (e.g. thrombophilia), may help to decide for cessation or continuation of post-interventional anticoagulation after treatment with venous stents.

OUTLINE OF THESIS

PART I – Endovenous management of acute deep vein thrombosis

The first part discusses current endovenous management of acute iliofemoral deep vein thrombosis (chapter 1).

PART II: – Anticoagulation management and recurrent venous thromboembolism

The second part describes post-interventional anticoagulation management, recurrent venous thromboembolism and associations with thrombophilia and left iliac vein compression syndrome in patients with venous stents for acute deep vein thrombosis and post-thrombotic syndrome (chapter 2).

PART III – Long-term results after venous stenting for acute deep vein thrombosis and post-thrombotic syndrome

The third part is focused on long-term outcomes after treatment with deep venous stents for acute deep vein thrombosis and post-thrombotic syndrome. Patency outcomes and causes for re-intervention are highlighted in this part (chapter 3). Quality of life after treatment with deep venous stents for acute deep vein thrombosis (chapter 4A) and post-thrombotic syndrome (chapter 4B) are also discussed.

PART IV – Inflow disease in post-thrombotic syndrome

The fourth part describes inflow disease of the femoral vein and/or deep femoral vein and patency outcomes in patients stented for post-thrombotic syndrome (chapter 5).

PART V – Extraordinary cases of deep venous disease

The last part describes extraordinary cases of deep venous stenting. Chapter 6 provides an overview of spontaneous iliac vein rupture, a rare but frequently lethal condition. Chapter 7 describes a patient stented for complaints of exercise intolerance due to vena cava atresia. Chapter 8 describes a rare case of cauda equina syndrome caused by ilio caval venous thrombosis, with successful resolution after treatment with venous stents.

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PART I

ENDOVENOUS MANAGEMENT OF ACUTE DEEP VEIN THROMBOSIS



Treatment of iliofemoral deep vein thrombosis: challenges, opportunities, and future perspectives

(Phlebology Journal, 2023)

van Rijn MJ, Bakas JM Treatment of iliofemoral deep vein thrombosis: challenges, opportunities, and future perspectives. Phlebology. 2023 Aug;26-34. No.109.

ABSTRACT

Acute iliofemoral deep vein thrombosis (DVT) is more symptomatic than a thrombosis distal to the common femoral vein and increases the risk of post-thrombotic syndrome (PTS), which reduces quality of life, and increases medical costs. To provide the best possible medical care, it all starts with identifying iliofemoral DVT. This will be achievable when visualizing the most upper thrombus part becomes standard practice. Treatment should be done by a multidisciplinary team encompassing lifestyle changes to compression therapy and adequate anticoagulation. In addition, early clot removal may lower the risk of PTS. Knowing which patients will benefit most is still unpredictable. New thrombectomy devices aim to restore patency without the use of thrombolysis. This may lower the threshold to consider a patient for early clot removal but may increase overtreatment. That is why it is equally important to focus future research on establishment of an accurate definition of PTS, a reliable prediction model to identify those who benefit from endovenous treatment, and to standardize post-interventional anticoagulation. Intensive collaboration between medical disciplines must therefore be continued during the complete pathway, from referral to long-term follow-up. In an aging population with a rapid increase in obesity and sedentary lifestyle, prioritizing the need for appropriate care for iliofemoral DVT patients is key.

INTRODUCTION

Approximately a quarter of deep venous thrombosis (DVT) is localized in the iliac and/or common femoral veins (CFV), also referred to as iliofemoral DVT.¹ Acute symptoms and signs of iliofemoral DVT often involve both the upper and lower part of the leg and are more severe compared with a DVT distal to the CFV. Also, the risk for developing chronic complaints related to postthrombotic syndrome (PTS) is increased.^{2,3} Various symptoms and signs related to deep venous obstruction and/or reflux may arise, starting from months to even years after the initial DVT.⁴ The incurability, chronicity, and severity of symptoms makes it one of the worst long-term complications. Therefore, adequate treatment of iliofemoral DVT involves PTS prevention, beside the acute symptom resolution.

Noninvasive treatment such as compression therapy and adequate anticoagulation, together with lifestyle changes like exercise and weight loss, should always be applied immediately after acute DVT and may also successfully relieve complaints of PTS.^{5,6} European Society of Vascular Surgery (ESVS) guidelines recommend an endovenous treatment for symptomatic patients with acute iliofemoral DVT.⁷ Beside resolution of acute symptoms and signs, it lowers the risk of PTS and improves quality of life (QOL) compared with noninvasive treatment.⁸ However, the reality is that in most hospitals treatment is still only conservative.

The increased use of endovenous treatment has changed the field for acute iliofemoral DVT treatment over the past decades. This article provides an overview of the challenges, opportunities, and future perspectives for these patients.

DEEP VENOUS THROMBOSIS

Incidence of acute DVT is approximately 1-2 per 1000 patients per year.⁹ Hypercoagulability, stasis, and endothelial damage (Virchow's triad) are key elements in DVT pathophysiology. New insights show many more involving factors like altered flow around the valves generating hypoxia, leading to endothelial activation and triggering adhesion molecules. In turn, there is recruiting of blood cells such as monocytes, neutrophils, and platelets. Monocytes and neutrophils activate coagulation through the extrinsic and intrinsic pathways, favoring thrombus formation and growth, and trapping more cells.¹⁰

Various risk factors can provoke a DVT, such as hormone therapy, pregnancy, immobilization, thrombophilia, recent surgery, endovenous procedures or place-

ment of central venous catheters, cancer, obesity, and advanced age.¹⁰ An “unprovoked” DVT arises without any preceding risk factors.

Distinction between “provoked” and “unprovoked” DVT is important in terms of prognostic and treatment implications.¹¹ Stopping anticoagulants might be considered after DVT with a transient risk factor, whereas life-long prescription is considered for persistent risk factors and unprovoked DVT.

Impaired blood flow in compression syndromes may also trigger DVT. Left iliac vein compression, caused by the May-Thurner syndrome (MTS), explains why most iliofemoral DVTs are left-sided.¹² The attributing risk of MTS to DVT, and whether it counts as a “provoking factor,” is unclear.

Anatomical sites of a DVT are divided into the calf veins, popliteal vein, femoral vein, CFV, and iliac veins with or without the inferior vena cava (IVC).¹³ An iliofemoral DVT without thrombus below the groin is uncommon. Therefore, the term “proximal” DVT can be misleading and should be avoided.¹³

DIAGNOSTICS

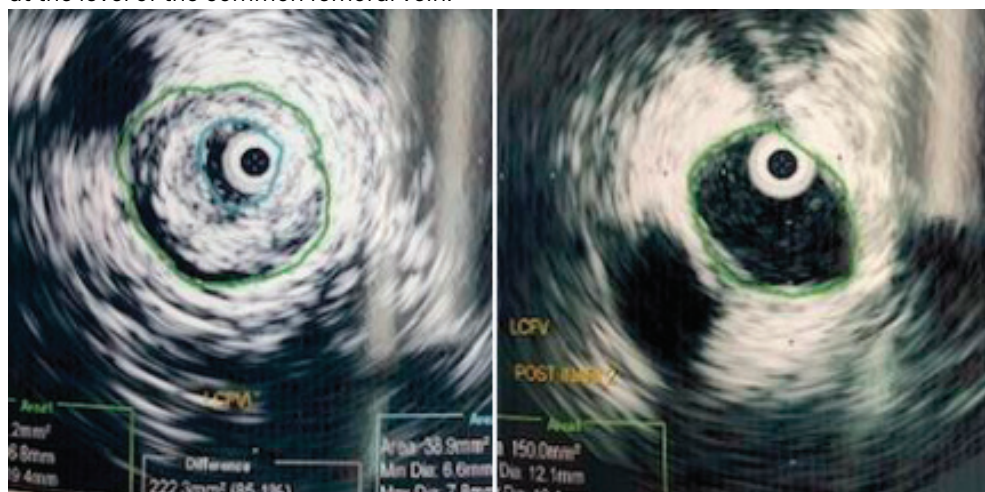
Management of suspected DVT starts with the assessment of patient history and physical examination. These factors are used to estimate the probability of acute DVT by using the Wells score. A D-dimer test and/or duplex ultrasound (DUS) can be added next.^{14,15} The preferred imaging modality for suspected DVT is DUS, but its accuracy depends on the technique used and the ultrasonographers’ experience. Combined color Doppler techniques have optimal sensitivity, whereas compression has optimal specificity for detecting DVT.¹⁶ Ideally, both techniques should be applied. In addition, 2- or 3-point compression scanning, and whole-leg ultrasound scanning. Both techniques may miss iliofemoral DVT when the upper thrombus part is not visualized. If thrombus is present in the femoral vein or CFV, the iliac veins should be visualized as well, with additional computed-tomography venography (CTV) or magnetic resonance venography (MRV) if DUS is inconclusive.¹⁷

Intravascular ultrasound (IVUS) is an increasingly performed imaging modality to visualize the extent of venous lesions during intervention for both acute and chronic cases.¹⁸ Because of its invasive nature, IVUS should not be used purely as a diagnostic. Peri-interventional use of IVUS provides useful complementary information, as multiplanar venography might underestimate the amount of residual thrombus during performance of a clot removal technique (*Figure 1*),

as well as residual obstruction.¹⁹ Also, IVUS discriminates between acute and chronic clots, the latter being more echogenic, surrounded by a thickened vein wall.²⁰ However, the recommendation for IVUS use during endovenous treatment is weak because the uncertain clinical and economic benefits require validation from randomized controlled trials (RCTs).²¹

Recently, a risk score was developed to distinguish iliofemoral DVT from all other suspected DVTs, with 77% sensitivity and 82% specificity.²² The model includes D-dimer levels, Wells score, age, and anticoagulation therapy, and may help to prioritize patients for immediate imaging to confirm or exclude iliofemoral DVT.

Figure 1. Peri-interventional intravascular ultrasound before and after thrombus removal at the level of the common femoral vein.



Left panel (within the green circle): hyperechogenic, older age, clot.

Right panel (within the green circle): a cleared vein without thrombus.

POSTTHROMBOTIC SYNDROME

Localization of DVT is important because thrombus extending into the CFV, iliac veins, and/or the IVC, may be considered for early clot removal.¹⁷ These DVTs are often more symptomatic than DVTs distal from the CFV and have an increased risk for PTS.² Various symptoms and signs of impaired venous outflow may arise in PTS, as a result of deep venous obstruction and/or reflux after DVT. It occurs in 20% to 50% of DVT, of which 5% to 10% result in severe PTS. Whereas PTS frequently arises within the first year, it may develop 10 to 20 years after the initial DVT.^{4,23} Common symptoms include pain, cramps, heaviness, paresthesia, and pruritis of the leg; common signs are edema, skin changes, redness, and pain during calf compression, with venous ulceration as one of the worst

clinical features.^{23,24} Preventing PTS, or reducing the severity, is important as PTS decreases QOL and imposes a burden on the health care system through high medical costs, lost workdays, and job loss.²³ Optimized anticoagulation, compression therapy, lifestyle changes (e.g. exercise and weight loss), and early thrombus removal may restore vessel and valve patency, thereby preventing (recurrent) DVT and worsening of PTS.

Various PTS scoring systems are available. The Villalta score combined with a venous disease-specific QOL score is the recommended golden standard²⁵; however, PTS definition and classification should be further optimized. The ideal scoring system is easy to use, reliable, and objective. It should take into account the broad spectrum of PTS manifestation, such as venous claudication,²⁶ and exercise intolerance,²⁷ which are both absent in current PTS scores.

ENDOVENOUS TREATMENT

The ESVS guidelines on the management of venous thrombosis (2021) recommend considering early thrombus removal for selected patients with symptomatic iliofemoral DVT, a class IIa, level A recommendation.⁷ The recommendation is based on reduced PTS risk after early clot removal for iliofemoral DVT. However, in most hospitals, treatment is still mainly conservative. Four randomized-controlled studies—TORPEDO (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion), CaVenT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis), ATTRACT (Acute venous Thrombosis Thrombus Removal with Adjunctive Catheter-directed Thrombolysis), and CAVA (Catheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT)—are randomized between: I) oral anticoagulants only; and II) early thrombus removal with catheter-directed thrombolysis (CDT), combined with (pharmaco)mechanical thrombectomy (PMT), and/or percutaneous transluminal angioplasty and stenting.²⁸⁻³¹ A meta-analysis showed that early thrombus removal was more effective than anticoagulation alone in preventing PTS (relative risk [RR] 0.67; 95% confidence interval [CI]: 0.45-1.00; $P=0.05$), but unfortunately with an increased major bleeding risk (RR: 5.68; 95% CI: 1.27-25.33; $P=0.02$).¹⁷ An increased risk reduction for PTS after endovenous treatment was shown during long-term follow-up of the CaVenT and CAVA trials,^{29,32} indicating the added impact of early clot removal over time.

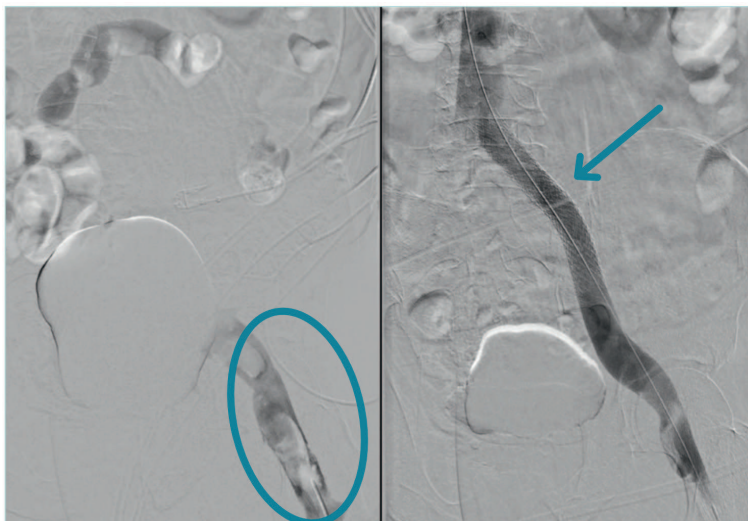
Venous stenting in addition to clot removal is successful in terms of venous patency with primary, assisted-primary, and secondary patency rates between 74% and 95%, 90% and 95%, and 84% and 100%, respectively after 12 months.^{33,34} Venous stenting should resolve compression points or obstructed segments from earlier (asymptomatic) thrombotic events.

Restoring venous patency is believed to lower the risk of re-thrombosis, although no RCT has been performed to confirm this. High patency and low migration rates suggest that there is little harm in performing additional stenting.^{33,34} At least 12% of all DVTs would be eligible for early clot removal¹³; however, overtreatment should be avoided. Patients are frequently symptomatic in the acute phase, but only a portion develops PTS over time. A prediction system is therefore needed to optimize patient selection for endovenous treatment.

Less-invasive treatment methods, such as compression therapy and daily walking, should always be encouraged to prevent PTS, stimulate venous recanalization, and increase inflow in case venous intervention is indicated during follow-up.^{35,36} Thrombectomy devices that are used without thrombolysis are dealing with the bleeding risks of endovenous treatment.³⁷ These devices are able to shorten hospitalization, as they aim to clear the veins in a single session (*Figure 2*). Patients can therefore be discharged the next day, preferably after confirming patency, but even same-day discharge might be possible.³⁸ The largest prospective series is the CLOUT registry (ClotTrieve[®] Outcomes, Inari Medical, Irvine, CA). In 250 patients (82% iliofemoral and/or caval DVT), no thrombolytics were used and 99.6% were treated in a single session. At 6 months, 24% of patients had PTS and all clinical outcomes improved, including the Revised Venous Clinical Severity Score, the numeric pain rating scale, and the EuroQoL Group 5-Dimension Self-Report Questionnaire.³⁷ *Figure 3* shows a ClotTrieve[®] device with extracted thrombus in it.

Early clot removal, using either PMT or CDT, is cost-effective and falls below the United Kingdom National institute threshold for cost-effectiveness.³⁹ An incremental cost-effective ratio of US \$20 000 per quality-adjusted life year makes CDT a cost-effective alternative to conservative treatment of iliofemoral DVT.⁴⁰ However, the long-term cost-effectiveness is higher for PMT than CDT.⁴¹ Lower costs for PMT compared with CDT are likely to be caused by shorter length of hospitalization and less invasive surveillance.⁴²

Figure 2. Venography in patient with acute deep vein thrombosis with complete occlusion of the iliac veins, before and after mechanical thrombectomy with ClotTriever® followed by venous stenting of the common iliac vein to overcome compression at the May Thurner point.



Left panel: a stop of contrast/flow proximal from the common femoral vein (CFV), with visible thrombus (blue circle) in the CFV.

Right panel: open common femoral and iliac veins and a stent (blue arrow) in the common iliac vein.

Figure 3. Mechanical thrombectomy device (ClotTriever®) with extracted thrombus.



THROMBUS AGE

Thrombus age is critical for treatment success because older collagen-rich thrombi are less susceptible to lysis than younger fibrin-rich thrombi.⁴³ Mean thrombolysis duration for >90% thrombus resolution was 23 hours for acute,⁴³ hours for subacute, and 85 hours for old clots.⁴⁴ CDT was almost 11 times more successful for acute and subacute clots than for older thrombi (odds ratio [OR]: 10.7; 95% CI: 2.1-55.5). Thrombus age was defined using MRV. Acute DVT was defined as an enlarged dilated vein with hypo-intense signal intensity sur-

rounded by a thin rim of contrast; subacute DVT, as an enlarged dilated vein with heterogeneous signal intensity surrounded by a thick rim of contrast; and older DVT, as a normalized caliber vein with heterogeneous and/or hypo-intense material without an evident rim of contrast and no apparent edema.⁴⁵

The most reliable DVT-staging method before endovenous treatment is unknown. Both magnetic resonance imaging and ultrasound elastography were previously used to distinguish between acute and chronic DVT, but the optimal method in terms of accuracy, cost-effectiveness, and reproducibility is yet to be found.⁴⁶ The CLOUT registry showed that chronicity assessed using symptom duration alone mismatched morphology-based chronicity in 55.1% of limbs ($P < 0.0001$), with 49.0% being more chronic than symptom duration suggested. Chronicity assessed using imaging mismatched the morphology chronicity in 17.5% of limbs ($P < 0.0001$).³⁸ Mechanical thrombectomy might lower the need for pre-interventional clot staging because of its favorable effectiveness of thrombus removal at various stages.³⁷

TECHNICAL ASPECTS

Open thrombectomy is performed by venotomy in the CFV with a Fogarty embolectomy catheter to evacuate the thrombus proximally and manual massage of the entire leg to evacuate the thrombus distally, or over-the wire catheterization in the direction of the foot, passing the valves, and then performing a thrombectomy. Open thrombectomy improves patency and reduces PTS compared with anticoagulant therapy alone.⁴⁷ Patency after 10 years was 83% compared with 41% after anticoagulant therapy only ($P < 0.05$). However, the open technique has become less popular with percutaneous options readily available.

Percutaneous techniques can be divided into CDT, mechanical thrombectomy, and PMT. *Table I* provides an overview of devices used for early thrombus removal in the venous system.⁴⁸ Often, the popliteal vein is punctured for access under DUS guidance. However, depending on the technique used and the thrombus extent, veins distal from the popliteal vein can be used for access too (for PMT devices with a small sheath size or for CDT), as well as the internal jugular vein (in case of deep femoral vein catheterization), or the CFV (up and over to catheterize the deep femoral vein, or if only the iliac or IVC is thrombosed). When choosing the puncture site, physicians should always anticipate venous stenting. Determining the degree of clot removal can be estimated using multiplanar venography during all different techniques, but IVUS might be more accurate. The same is true for determining whether postthrombotic obstruction and/or

compression syndromes have contributed to DVT and should be considered for stenting.¹⁹ Intravenous heparin is administered during intervention. Immediately after cessation of the procedure, low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOAC) should be prescribed to prevent re-thrombosis of cleared segments. Vitamin-K-antagonists (VKA) may be started as well, after bridging with LMWH. As soon as possible, patients should be encouraged to walk. Pneumatic compression devices stimulate venous return if patients are not mobilizing after the procedure. As long as the leg is swollen, compression therapy should be applied. After clots are completely removed and leg circumference is decreased, continuing compression therapy mainly depends on patient preference.

Table I. Devices for early thrombus removal in the venous system.

Company (alphabetical)	Product
<u>Abbott</u> [®]	§ Jeti
<u>AngioDynamics</u> [®]	§ AlphaVac System
<u>BD Interventional</u> [®]	§ Aspirex Mechanical Aspiration Thrombectomy System
<u>Boston Scientific Corporation</u> [®]	§ AngioJet Thrombectomy Catheter: Solent Omni, Proxi, ZelanteDVT, ClotHunter, and PE § Ekos and Ekos+
<u>Control Medical Technology</u> [®]	§ Control Mechanical Thrombectomy System § Control Mechanical Aspirator
<u>Inari Medical</u> [®]	§ ClotTrievers System § FlowTrievers System
<u>Penumbra, Inc.</u>	§ Indigo System
<u>(Peripheral Vascular)</u> [®]	§ Indigo system with lightning Aspiration
<u>Philips</u> [®]	§ QuickClear Mechanical Thrombectomy System
<u>Thrombolex, Inc.</u> [®]	§ Bashir Endovascular Catheter and S- B Endovascular Catheter
<u>Truvic, Inc.</u> [®]	§ Prodigy Thrombectomy System

Reference 48: Endovasc Today.

<https://evtoday.com/deviceguide/us/mechanical-thrombectomythrombolysis>

SURVEILLANCE

Iliofemoral DVT may cause valve destruction (reflux) or scarring of the vein (obstruction), leading to PTS. Monitoring symptoms and signs of PTS during surveillance is important because PTS might develop within months to even years.⁴ Treatment of PTS focuses on improving symptoms and signs, in the absence of a curative treatment.⁵ The incurability of PTS and severity of symptoms and signs emphasize the importance of preventing it from the start.

Optimal anticoagulation, immediate mobilization, and compression therapy are first line strategies for PTS prevention, but evidence for its efficacy is weak.⁶ Wearing elastic compression stockings (ECS) for at least 2 years was found to lower PTS incidence compared with patients who stopped wearing ECS.⁴⁹ However, wearing ECS for at least 6 months followed by individualized extension of treatment duration is noninferior to the standard 2 years in terms of PTS prevention, as shown by the IDEAL trial (Ideal Deep Venous Thrombosis Study).⁵⁰

Venous (stent) patency, residual obstruction, and venous reflux are evaluated using DUS. Peak flow velocity is combined with flow pattern analysis to diagnose, or rule out, stent occlusion and stenosis.⁵¹ If DUS is inconclusive, additional CTV should be considered, or even more invasive imaging like venography or IVUS with immediate intervention, when the suspicion of loss of patency is high. Stent patency could be referred to as primary patency, secondary patency, or permanent stent occlusion. Primary patency is the percentage of open stents without re-intervention. Secondary patency is the percentage of open stents after re-intervention. Permanent stent occlusions are occluded stents without further options to restore stent patency. Anticoagulant therapy compliance, thrombus burden, and poor venous flow are risk factors for reintervention.⁵² Re-interventions should ideally be prevented, or performed before vessel occlusion.⁵² Usually, follow-up is intensified in the first weeks after intervention, gradually diminishing (after uncomplicated procedures) over time until once a year or once every other year.

ANTICOAGULATION THERAPY

Evidence-based guidelines providing optimal anticoagulant therapy after venous stenting are lacking.⁵³ Patients usually receive a DOAC, or LMWH switched to a VKA. Adjunctive use of antiplatelet agents does not seem useful, based on the underlying pathophysiology and clinical experience.⁵⁴ It did not affect outcomes after venous stenting for acute DVT, including recurrence of DVT, patency, incidence of PTS, and restenosis.⁵⁵

Effectiveness and safety of post-interventional treatment with DOAC and VKA is similar for acute DVT patients⁵⁶; however, treatment with VKA provides time within therapeutic range, providing information about compliance. Anticoagulation therapy is considered for at least 3 to 6 months after acute DVT in general. Extension of treatment duration with anticoagulants depends on the presence or absence of provoking DVT factors.⁵⁷ Anticoagulants might be stopped if a transient provoking factor is present. Hypothetically, the introduction of venous

stenting has transformed MTS into a “transient” factor. The ESVS guidelines recommend that duration of anticoagulant therapy after early thrombus removal (with or without venous stenting) should be based on the primary indication for anticoagulation and judged by the treating physician.¹⁷ Evidence supporting the optimal length of anticoagulant treatment after successful venous stenting is lacking.

CHALLENGES, OPPORTUNITIES, AND FUTURE PERSPECTIVES

Iliofemoral DVT increases the risk for PTS, a devastating, lifelong syndrome that lowers QOL and burdens the health care system.²³ Optimal treatment is key in preventing PTS, but several hurdles still need to be overcome. First of all, patients with an iliofemoral DVT should be identified. Physicians involved in the diagnostic phase of DVT should therefore be trained to always visualize the upper thrombus part. Next, these patients need to get referred to expert centers to discuss all treatment options, including early clot removal. This requires better, more intensive collaboration between vascular surgeons, interventionalists, phlebologists, dermatologists, internal medicine doctors, and general practitioners. The reality, however, is that most hospitals still only consider a conservative treatment for these patients.

Fortunately, (deep) venous disease is getting increased interest at conferences around the world. Increased awareness is also achieved through social media, at the level of physicians and by patients themselves. Interests from different medical specialists brings the opportunity for optimized care in a multidisciplinary approach.

Next, an objective, reliable, and easy to use scoring system for definition and classification of PTS should be developed, taking into account “typical” signs and symptoms, but also complaints such as exercise intolerance and venous claudication.¹⁷ Studies aiming to prove benefits of early clot removal should have a much longer follow-up than the typical first year, as PTS may take years to develop.⁴ New studies should also overcome the flaws of previous RCTs like low technical success, low rate of stenting, the use of nondedicated venous stents, and the absence of DUS follow-up.

Another challenge is motivating healthy lifestyles in an aging population with a rapid increase in obesity and a sedentary lifestyle. Lifestyle education is a huge part of patient care. With increased popularity of activity-tracking devices, mo-

tivation for exercise may become more easily accessible, as well as more playful and fun.

Opportunities arise from the evolution of new devices, presumably lowering the threshold for considering endovenous treatment. Aspiration devices without thrombolysis should, ideally, shift endovenous treatment to a low-risk technique, which also seems feasible for management of older thrombi.^{37,38} The DEFIANCE trial randomizes between mechanical thrombectomy with the ClotTriever® and anticoagulation only and will hopefully further reveal the impact of early clot removal on PTS prevention. Another exciting discovery is the involvement of inflammation and microRNAs in the pathophysiology of DVT, which might lead to therapeutic targets for drug development.¹⁰

Clinicians must aim to give (iliofemoral) DVT patients a clot- and PTS-free future, with joined forces from all medical specialties involved. Venous thrombosis patients deserve just as much attention as those with arterial occlusions. With so many new and exciting developments in the field of acute iliofemoral DVT, it is our strong belief that this can and will happen.

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PART II

ANTICOAGULATION MANAGEMENT AND RECURRENT VENOUS THROMBOEMBOLISM



Anticoagulation Management and Recurrent Thrombosis after Venous Stenting for Deep Vein Thrombosis and Post-thrombotic Syndrome

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WHAT THIS PAPER ADDS

This retrospective, single center study evaluated anticoagulation management (and risk factors) for recurrent venous thromboembolism (VTE) in patients with venous stents for deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS). Recurrent VTE was frequent (38%): almost always (93%) in-stent re-thrombosis. Recurrent VTE after cessation of anticoagulation was 25%: stent patency was restored in all these cases. Thrombophilia was identified by clinically indicated tests in 20 patients. Additional testing for scientific purposes identified five additional patients with thrombophilia. No risk factors for recurrent VTE were identified in multivariable analysis. Decision models regarding the duration of anticoagulation management require further prospective study.

ABSTRACT

Objective:

There are no evidence-based recommendations for anticoagulation management after venous procedures. This study aimed to evaluate how anticoagulation was managed after venous stenting for deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS).

Methods:

Patients who underwent venous stenting for DVT or PTS between May 2006 to November 2021 were screened for inclusion. The primary endpoint was post-interventional management of anticoagulation or antiplatelet therapy. Secondary endpoints were recurrent venous thromboembolism (VTE) and potential risk factors (e.g., thrombophilia and left iliac vein compression syndrome (LIVCS)). All patients underwent thrombophilia tests for the study's purpose. Descriptive statistics were applied for anticoagulation management. Recurrent VTE free survival was estimated using Kaplan-Meier methods (log rank). Binary logistic regression was conducted to estimate risk factors for recurrent VTE.

Results:

Seventy nine patients were included: 41 DVT and 38 PTS. Until last follow-up (median 250 weeks, interquartile range [IQR] 158, 439), anticoagulation was continued for 57 (72%), and stopped for 22 (28%) patients. Post-interventional recurrent VTE occurred in 30 (38%) patients (32% DVT [n= 13]; 45% PTS [n= 17]) after a median duration of 11 weeks (IQR 3, 129), of which 93% were in-stent re-thrombosis. Primary patency was 62% (n= 49) and secondary patency was 94% (n= 74). Most recurrent VTEs (87%) occurred during anticoagulant therapy. Anticoagulation was re-started in all five patients with recurrent VTE after cessation of anticoagulant therapy. Anticoagulant therapy remained stopped in the absence of recurrent VTE (n= 17). Thrombophilia seemed to be statistically significantly associated with increased recurrent VTE (odds ratio 3.02, 95% confidence interval 1.13 – 8.07; p= .027) and left iliac vein compression syndrome with decreased recurrent VTE (odds ratio 0.30, 95% confidence interval 0.10 – 0.90; p = .032). Significance was lost in multivariable analysis.

Conclusion:

Recurrent VTE occurred in 38% patients (32% DVT; 45% PTS) almost always (93%) in-stent re-thrombosis. Although approximately a quarter of patients experienced VTE after cessation of anticoagulation, stent patency was restored in all cases. No risk factors for recurrent VTE were identified.

Keywords: Anticoagulation; Deep Vein Thrombosis; Venous Thrombosis; Thrombophilia; Endovascular Procedures; Venous stenting.

INTRODUCTION

Iliofemoral deep vein thrombosis (DVT) includes thrombosis of the iliac veins and/or common femoral vein, with or without other associated veins.^{1,2} These DVTs are frequently left-sided due to left iliac vein compression syndrome (LIVCS), in which the right common iliac artery compresses the left common iliac vein (CIV) against the lumbar spine.³

Post-thrombotic syndrome has been reported in approximately 20-50% after DVT.⁴⁻⁷ Localisation of DVT is an important predictor for PTS development, with increased PTS-risk after iliofemoral DVT.^{6,7} Although conservative management remains the gold standard, early thrombus removal may be applied in symptomatic iliofemoral DVT to resolve acute complaints and possibly prevent PTS (with or without stents).^{8,9} In elective settings, venous stents can be used for PTS treatment.^{10,11} Post-intervention anticoagulation therapy is recommended to maintain (stent) patency, but the optimal type, dose, and duration remain unclear.¹²⁻¹⁴

There are no evidence based recommendations for duration of anticoagulation treatment after deep venous procedures. Treatment duration generally depends on presence of DVT (transient or persistent) provoking factors.¹⁵ The optimal duration of anticoagulant treatment is unknown owing to limited data.¹² There is a lack of consensus on whether LIVCS is a DVT provoking factor, and whether it affects anticoagulation treatment duration after adequate venous stenting. Cessation of anticoagulation therapy three to 12 months after treatment has been suggested to be safe in cases with adequate inflow and outflow, preserved patency, and absence of persistent prothrombotic disorders.¹⁶ The role of thrombophilia in this setting is uncertain.¹⁷ Post-interventional management of anticoagulation, recurrent venous thromboembolism (VTE), and risk factors were evaluated in patients with venous stenting for DVT and PTS.

MATERIALS & METHODS

Patients

This retrospective, single center cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹⁸ Consecutive patients with venous stents for DVT or PTS treated at an academic hospital centre from May 2006 (first procedure) to November 2021 (timepoint of research analysis) were screened for inclusion. Patients were identified from the patient electronic data system, including “hospital treatment codes” and data

from visits at the outpatient clinic. Previous publications described patency, patient-reported outcomes, and inflow disease of this cohort.¹⁹⁻²² Treatment of DVT involved the iliofemoral tract with or without associated veins, with severe persistent symptoms under standard DVT treatment. They underwent catheter directed thrombolysis and/or percutaneous thrombectomy followed by venous stenting in case of a significant stenosis (>50%) on venography and/or intravascular ultrasound (IVUS). From 2017, IVUS was used for all procedures. Venous stents were positioned for iliofemoral obstruction in moderate to severe PTS cases (Villalta score > 10).⁶ Dedicated venous stents were used for most procedures, with non-dedicated stents only used before 2017. The length and number of stents were summed for all patients (initial procedure), without correcting for overlap. More procedure details have been described in a previous publication.²⁰ Informed consent was sought for study participation at various time points after stenting. Exclusion criteria were missing informed consent, venous stents placed in palliative care setting, uncertainty about DVT classification, and non-thrombotic iliac vein lesions. Follow-up of stent patency, anticoagulation treatment, and recurrent VTE was completed until February 2024 or until loss-to-follow-up. Some patients had already undergone thrombophilia tests (clinical indication). All others tests were performed for the study purpose after informed consent. The study was approved by the local Medical Ethics Committee (MEC: 2020-0429).

Classification of index deep vein thrombosis

The index DVT was classified for all DVT and PTS patients. The index DVT was “provoked” if a clear preceding clinical risk factor was present, such as immobility, recent surgery, hospitalisation for more than three days, active malignancy, pregnancy, oral contraceptives, or long-distance air travel (more than eight hours). These factors were absent in “unprovoked” DVT. Patients in whom the index DVT was a recurrent DVT (either ipsilateral or contralateral), were classified as ‘recurrent DVT’. LIVCS was not considered a provoking factor in the classification.

Left iliac vein compression syndrome

Presence of LIVCS was scored retrospectively by two authors (J.M.B. and M.J.E.v.R) using all available pre- and perioperative imaging: computed tomography venography (CTV), magnetic resonance venography (MRV), venography and/or IVUS. In general, CTV was performed for DVT and MRV for PTS patients. For DVT, LIVCS was present if a >50% stenosis remained in the left CIV after thrombus removal. Left iliac vein compression was deemed absent if the left CIV was patent, the thrombus involved the inferior vena cava (IVC), or if DVT was right-sided. For PTS, LIVCS was present if only the CIV was stenosed and

absent in right-sided or bilateral cases, as well as cases with IVC involvement, sometimes causing uncertainty about LIVCS presence. Unclear LIVCS was classified as “possible”.

Post-intervention management of anticoagulation

“Post-intervention” management included anticoagulation type and duration after the primary stenting procedure. Anticoagulation and antiplatelet therapy were evaluated until last follow-up. Collected data included all types and doses of anticoagulants and antiplatelets. Anticoagulants considered were unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), vitamin K-antagonists (VKA) and direct-oral-anticoagulants (DOACs). Antiplatelets considered were acetylsalicylic acid, carbasalate calcium, clopidogrel or other P2Y12-antagonists. Since 2017, a multidisciplinary team including a hematologist, re-evaluated anticoagulation strategies for all patients after one year. Cessation was considered in case of 1) provoked DVT if the provoking factor was resolved, 2) unprovoked DVT in the presence of LIVCS resolved with a stent. In both scenarios, primary patency of the stent(s) was required, with sufficient in- and outflow.

Endpoints

Recurrent venous thromboembolism

Recurrent VTE was defined as recurrent symptomatic ipsilateral DVT (including stent thrombosis/stenosis), contralateral DVT and pulmonary embolism (PE). Confirmation by appropriate imaging was required. Stent patency was evaluated by duplex ultrasound (DUS) one day after venous stenting, at two, six, and twelve weeks, six months, and annually thereafter. The same protocol was followed after re-intervention. Extra DUS was performed for symptomatic patients. Technical causes for stent occlusion, such as stent compression and migration, were not considered recurrent VTE.

Stent patency and inflow disease

Primary patency was defined as an open stent without re-intervention. Secondary patency was defined as an open stent after a re-intervention. Re-interventions were performed for occluded venous stents or stenoses (>50%): thrombolysis, in-stent stenting, stent extension and/or percutaneous transluminal angioplasty. Permanent stent occlusion refers to (unsuccessfully re-intervened) occluded stents, without options to restore patency (e.g. because of insufficient inflow). Inflow disease was defined as presence of post-thrombotic changes in the deep femoral vein (DFV) and/or femoral vein (FV) on pre- and periopera-

tive imaging (venography, CTV, MRV, and/or DUS).¹⁹ For patients with bilateral stents, the limb with the “worst” inflow or patency was used.

Thrombophilia

Hereditary thrombophilia that was assessed included antithrombin deficiency, protein C deficiency, protein S deficiency, factor-V-Leiden mutation, and prothrombin G20210A-mutation. Antiphospholipid antibodies were assessed by lupus anticoagulant (LAC), anticardiolipin (aCL) IgM- and IgG-antibodies, and beta-2-glycoprotein (β 2GP) IgM- and IgG-antibodies. Antiphospholipid syndrome (APS) was diagnosed based on one or more positive antiphospholipid antibodies at two different time points at least 12 weeks apart, according to the revised Sapporo criteria,²³ and history of VTE.

Statistical analysis

Descriptive statistics included counts with percentages, medians with interquartile ranges (IQRs) and means with standard deviations. Event free survival from recurrent VTE was analysed using Kaplan-Meier survival, with log rank (Mantel-Cox) test. Binary logistic regression assessed covariables associated with recurrent VTE. Covariables tested were age (binary, cutoff median), sex, indication (DVT or PTS), thrombophilia, inflow disease, stents across the inguinal ligament, stent length, number of stents, DVT classification, and LIVCS. Variables with $p < .10$ on univariate analysis were introduced into a multivariate analysis. Missing variables were excluded from the analysis. Patients were censored after loss to follow up. Statistical analyses were performed using IBM SPSS software version 28.0.1.0 (IBM, Armonk, NY, USA).

RESULTS

Patients

From May 2006 until November 2021, 117 patients with venous stents for DVT or PTS were identified, and 79 were included (Figure 1). Primary patency was 62% ($n = 49$) and secondary patency was 94% ($n = 74$) at last date of follow-up. Median follow-up was 250 weeks (IQR 158, 439). Characteristics of included patients stented for DVT ($n = 41$) and PTS ($n = 38$) are outlined in [Table 1](#).

Figure 1. Flowchart of patient inclusion

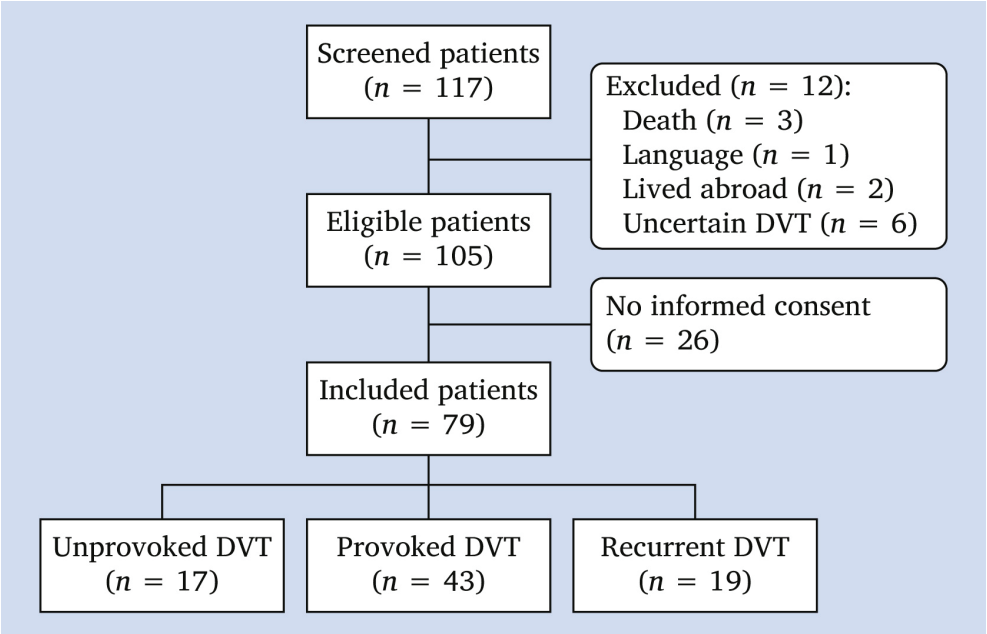


Table 1. Characteristics of included patients (n = 79) with stents for deep vein thrombosis and post-thrombotic syndrome.

Characteristics	Deep vein thrombosis (n = 41)	Post-thrombotic syndrome (n = 38)
Age – y	36 (26, 50)	46 (35, 55)
Women	25 (61)	32 (84)
Stent across the inguinal ligament		
Yes, extending into the CFV	7 (17)	29 (76)
No, not extending into the CFV	34 (83)	9 (24)
Stent location		
Left	32 (78)	28 (74)
Right	1 (2)	3 (8)
Bilateral	4 (10)	7 (18)
Inferior vena cava only	4 (10)	0 (0)
Stent characteristics		
Length – mm	100 (90, 180); n = 2*	245 (208, 305); n = 4*
Stents – n	2 (1, 2); n = 0*	3 (2, 3); n = 2*
Left iliac vein compression syndrome		
Yes	25 (61)	4 (11)
No	13 (32)	18 (47)
Possibly	3 (7)	16 (42)
Classification of deep vein thrombosis		
Unprovoked	13 (32)	4 (11)
Provoked	24 (59)	19 (50)
Recurrent	4 (10)	15 (40)
Coagulation disorders		
Thrombophilia presence	10 (24)	15 (40)
Inflow disease		
Yes	6 (15); n = 2*	23 (66); n = 3*
Follow up		
Time between stenting and last follow up – wk	202 (127, 277)	402 (189, 567)

Data are presented as n (%) or median (interquartile range). CFV = common femoral vein IQR.

* missing values because of unavailable data.

Classification of index deep vein thrombosis for the whole cohort

Characteristics of patients with unprovoked (n= 17; 22%), provoked (n= 43; 54%), and recurrent DVT (n= 19; 24%) are shown in Table 2. Women often had provoked (77%) or recurrent DVT (84%). Most stents were left sided across all DVT classifications. LIVCS was common in unprovoked DVT (n= 12, 71%). In the provoked group, n= 12 patients (33%) had LIVCS. Inflow disease was unavailable for five patients (6%) because of unavailable or insufficient imaging.

Table 2. Characteristics and outcomes per classification type of deep vein thrombosis.

Characteristics	Unprovoked DVT (n = 17)	Provoked DVT (n = 43)	Recurrent DVT (n = 19)
Age – y	42 (26, 58)	42 (29, 52)	41 (27, 50)
Women	8 (47)	33 (77)	16 (84)
Stent indication			
DVT	13 (77)	24 (56)	4 (21)
Post-thrombotic syndrome	4 (24)	19 (44)	15 (79)
Stent location			
Left	15 (88)	32 (74)	13 (68)
Right	0 (0)	3 (7)	1 (5)
Bilateral	0 (0)	6 (14)	5 (26)
Inferior vena cava only	2 (12)	2 (5)	0 (0)
Stent characteristics			
Length – mm	92 (80, 175); n = 1*	220 (100, 300); n = 2*	235 (159, 328); n = 3*
Stents – n	1 (1, 2)	2 (2, 3)	3 (2, 4); n = 2*
Left iliac vein compression syndrome			
Yes	12 (71)	14 (33)	3 (16)
No	5 (29)	19 (44)	7 (37)
Possibly	0 (0)	10 (23)	9 (47)
Thrombophilia presence			
Yes	3 (18)	10 (23)	12 (68)
Inflow disease			
Yes	4 (24)	17 (43); n = 3*	8 (47); n = 2*
Stent patency at last follow up			
Primary	13 (77)	24 (56)	12 (63)
Secondary	16 (94)	41 (95)	17 (90)
Permanent occlusion	1 (6)	2 (5)	2 (11)

DVT= deep vein thrombosis. Q1: first quartile.Q3: third quartile. * missing values because of unavailable data.

Thrombophilia

Thrombophilia was present in 25 patients (32%), [Table 2](#). Thrombophilia types included: heterozygous factor V Leiden mutation (n= 12), heterozygous prothrombin G20210A mutation (n= 5), antiphospholipid syndrome (n= 4), antithrombin deficiency (n= 1), protein S deficiency (n= 1), homozygous factor V Leiden (n= 1), and double thrombophilia (n= 1; heterozygous prothrombin G20210A mutation and antithrombin deficiency). Thirty tests were for a clinical indication. Forty nine (additional) tests were performed for study purposes; the tests showed that there were five additional patients (10%) with thrombophilia diagnoses (four with heterozygous factor V Leiden mutation and one with heterozygous prothrombin G20210A mutation). Most additionally diagnosed patients were women (four of five), and stented for DVT (four of five), and all five were categorised as provoked DVT.

Post-interventional management of anticoagulation (first year)

All patients were treated with therapeutic LMWH and after two weeks switched to VKA with targeted international normalised ratio (INR) of 2.0 – 3.0 (n= 78, 99%), or DOAC (n= 1, 1%). Additional antiplatelet therapy was standard practice in early years of endovenous procedures: prescribed in 19 patients (24%) with median duration of six weeks (IQR 6, 9). After one year, 71 (90%) continued therapeutic anticoagulation therapy: 97% (n= 69) VKA, 1% (n= 1) DOAC, and 1% (n= 1) LMWH). Six patients (8%) stopped because of bleeding complications or non-compliance. Two patients (3%) were lost to follow-up before one-year at the evaluation time point (continuing therapeutic anticoagulation (VKA) until 23 and 46 weeks).

Long-term management of anticoagulation (more than one year)

Patients who continued and stopped anticoagulant therapy are shown in [Table 3](#). At last follow-up 57 patients (72%) continued anticoagulation therapy and 22 patients (28%) had stopped. For 17 patients, anticoagulant therapy was stopped after physician approval. Four patients had bleeding complications before cessation of anticoagulant therapy (hematuria, hematoma and/or heavy menstrual bleeding). One patient stopped against medical advice. Patients in whom anticoagulation stopped often had provoked DVT (68%), LIVCS (59%) and a primary patent stent (95%).

Table 3. Characteristics of patients in which anticoagulation was continued indefinitely, or was stopped after a minimum of one year.

Characteristics	Continued ACT (n = 57)	Stopped ACT (n = 22)
Age – y	41 (26, 51)	44 (33, 59)
Women	38 (67)	19 (86)
Classification of DVT		
Unprovoked	11 (19)	6 (27)
Provoked	28 (4)	15 (68)
Recurrent	18 (32)	1 (5)
Stent indication		
DVT	28 (49)	13 (59)
Post-thrombotic syndrome	29 (51)	9 (41)
Stent location		
Left	41 (72)	19 (86)
Right	1 (2)	3 (14)
Bilateral	11 (19)	0 (0)
Inferior vena cava only	4 (7)	0 (0)
Stent characteristics		
Length – mm	200 (100, 300); n = 5*	170 (80, 245) n = 1*
Stents – n	2 (1, 3) n = 2*	2 (1, 2)
Left iliac vein compression syndrome		
Yes	16 (28)	13 (59)
No	25 (44)	6 (27)
Possibly	16 (28)	3 (14)
Thrombophilia presence		
Yes	20 (35)	5 (23)
Inflow disease		
Yes	24 (45); n = 4*	5 (24); n = 1*
Stent patency†		
Primary	31 (54)	21 (95)
Secondary	21 (37)	1 (5)
Permanent occlusion	5 (9)	0 (0)

Data are presented as n (%) or median (interquartile range). ACT = anticoagulant therapy; DVT = deep vein thrombosis.

* Missing values because of unavailable data.

† Stent patency reported at last date of follow-up for continued ACT, and at time of cessation of anticoagulants for stopped ACT.

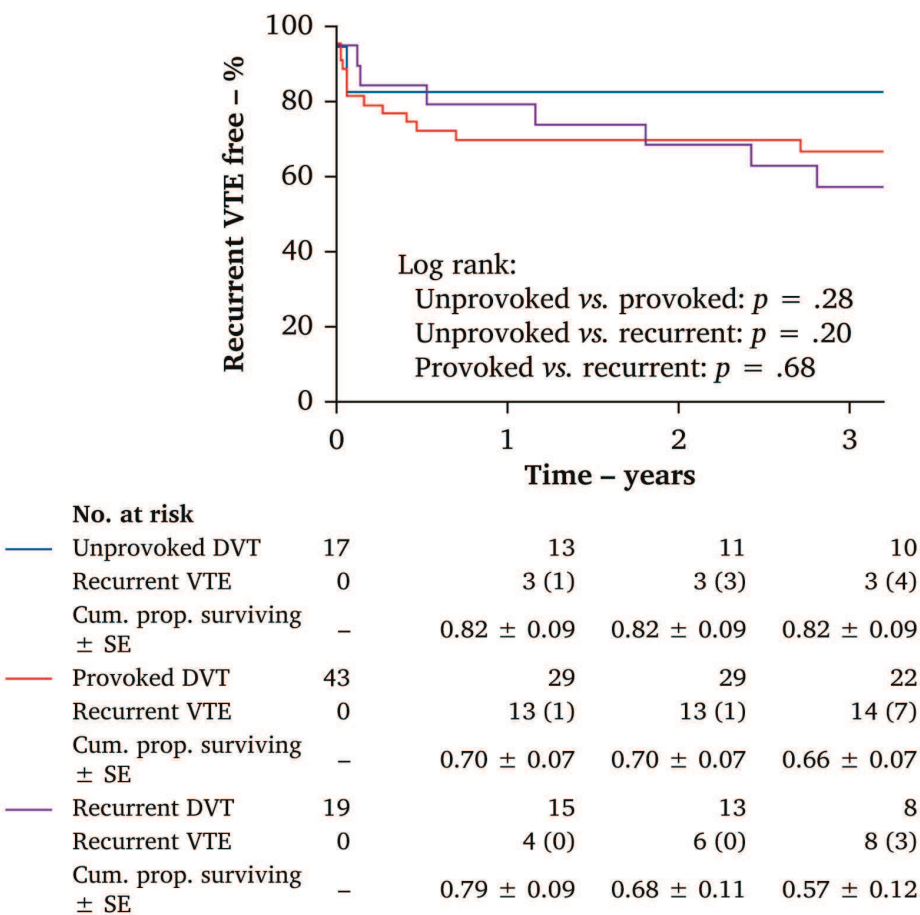
Recurrent venous thromboembolism

Recurrent VTE was 38% (n= 30) after a median post-intervention duration of 11 weeks (IQR: 3-129): 32% for DVT (n= 13) and 45% for PTS (n= 17). Most recurrent VTE occurred within the first year (67%; n= 20), mostly (93%) in-stent re-thrombosis. The three year cumulative incidence of recurrent VTE was 32% (25 patients, n= 22 stent patency loss). Eight recurrent VTEs occurred after three years follow up. Most patients (87%) used anticoagulant therapy at the time of recurrent VTE. Recurrent VTE included partial or complete stent thrombosis (n= 28, for one with concomitant contralateral DVT), contralateral DVT or distal vein DVT (n= 1), and PE (n= 1).

Figure 2 shows the three year recurrent VTE free survival without significant differences across DVT classifications. Similarly, for LIVCS, three year recurrent VTE free survival did not show statistically significant differences (p= .11; Fig. 3). Thrombophilia was associated with increased recurrent VTE risk during three year follow-up (p=.008; Fig. 4). Statistical significance was lost (log rank: p= .070) in a subanalysis of patients with in stent re-thrombosis (n= 22).

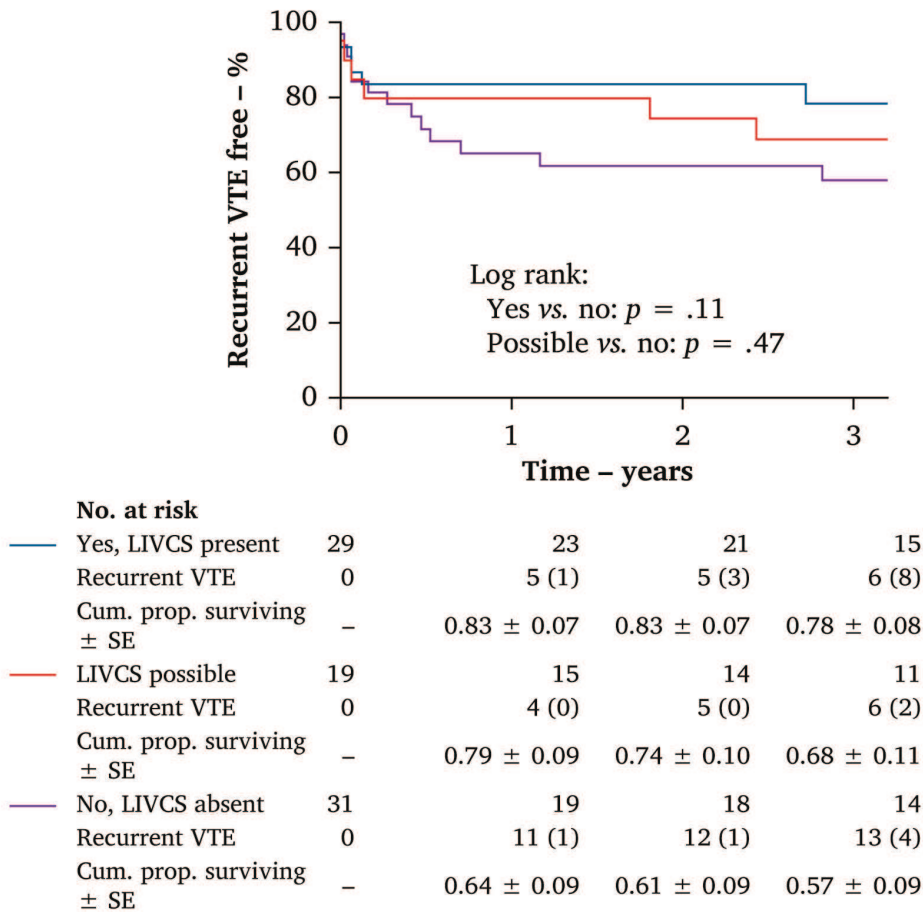
Covariables for recurrent VTE were evaluated in an univariable analysis: thrombophilia (odds ratio [OR] 3.02, 95% confidence interval [CI] 1.13 – 8.07; p= .027) seemed significantly associated with increased risk of recurrent VTE, whereas LIVCS seemed associated with reduced risk of recurrent VTE (OR: 0.30, 95%CI 0.10 – 0.90, p= .032). Neither remained statistically significant after multivariable analysis, Table 4.

Figure 2. Cumulative Kaplan–Meier estimate of three year event free survival from recurrent venous thromboembolism (VTE) per type of index deep vein thrombosis (DVT).



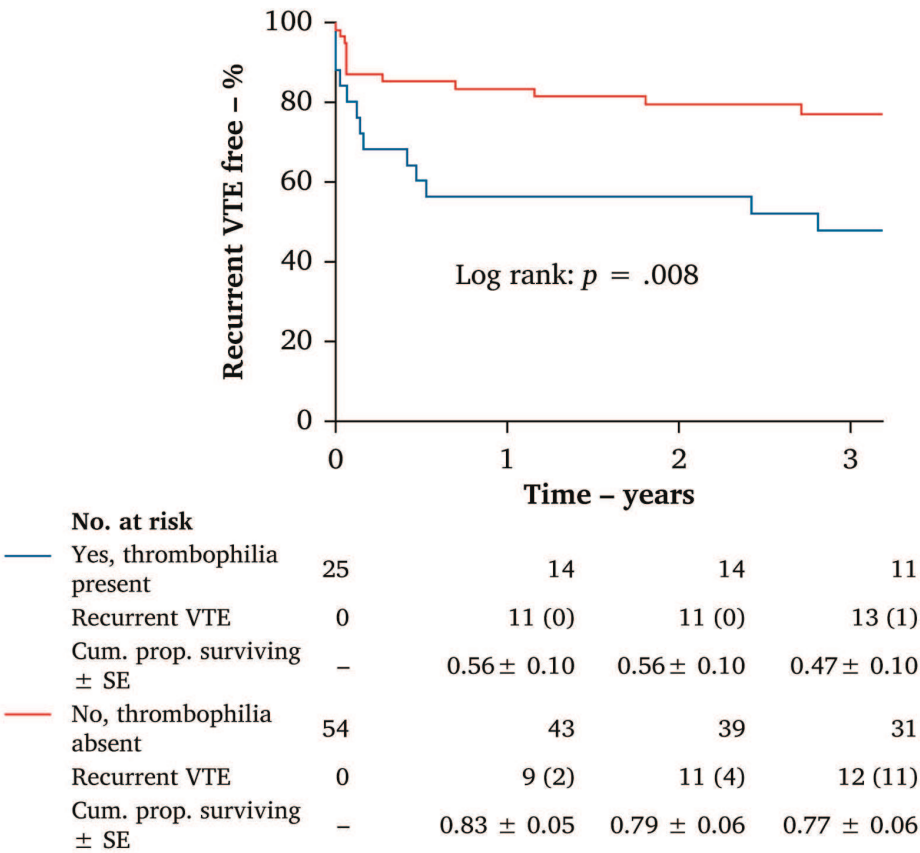
SE = standard error.

Figure 3. Cumulative Kaplan–Meier estimate of three year event free survival from recurrent venous thromboembolism (VTE) in patients with and without left iliac vein compression syndrome (LIVCS).



SE = standard error.

Figure 4. Cumulative Kaplan–Meier estimate of three year event free survival from recurrent venous thromboembolism (VTE) in patients with and without thrombophilia.



SE = standard error.

Table 4. Uni- and multivariable binary logistic regression for recurrent venous thromboembolism.

Variable	OR (95% CI)	p value
Univariable	Patients (n = 79)*	
Age, above median (≥41 years)	0.60 (0.24–1.51)	.28
Female sex	1.10 (0.40–3.05)	.86
DVT	0.57 (0.23–1.44)	.24
Thrombophilia	3.02 (1.13–8.07)	.027
Inflow disease DFV/FV	1.63 (0.62–4.24)	.32
Stent across the IL	2.07 (0.82–5.20)	.12
Classification of DVT		
Provoked	1.0 (ref.)	–
Unprovoked	0.52 (0.14–1.87)	.32
Recurrent	1.88 (0.63–5.59)	.26
LIVCS		
No	1.0 (ref.)	–
Possible	0.55 (0.17–1.76)	.31
Yes	0.30 (0.10–0.90)	.032
Stent length, above median (>180 mm)	2.07 (0.79–5.43)	.14
Stents, above median (>n = 2)	1.88 (0.71–4.96)	.21
Multivariable	Patients (n = 60)†	
Thrombophilia	3.14 (0.94–10.48)	.062
LIVCS		
No	1.0 (ref.)	–
Possible		
Yes	0.38 (0.12–1.19)	.10

CI = confidence interval; DFV = deep femoral vein; DVT = deep vein thrombosis; FV = femoral vein; IL = inguinal ligament; LIVCS = left iliac vein compression syndrome; OR = odds ratio; REF = reference.

* Five patients were excluded because of insufficient data about inflow disease, six for stent length, and two for the number of stents.

† Nineteen patients with “possible” LIVCS were excluded from multivariable analysis.

Restart of anticoagulant therapy

Anticoagulation therapy was restarted in five out of 22 patients (23%) who stopped anticoagulation after in-stent stenosis or occlusion. Four patients had primary stent patency during cessation of anticoagulant therapy, and one patient had secondary stent patency. All five had provoked DVT. Three were stented for DVT and two for PTS. Four patients were woman. Heterozygous factor V Leiden was present in two patients. LIVCS was present in one patient, and inflow disease in two.

Patency was successfully restored or maintained in all five patients (four after re-intervention). Three patients underwent thrombolysis for occlusion: one patient with concomitant contralateral DVT thereafter followed by stent placement creating a double barrel. The last two patients had a >50% in-stent stenosis: one was left untreated, and the other treated with percutaneous transluminal angioplasty.

DISCUSSION

Recurrent VTE occurred in 38% of patients after venous stenting (32% for DVT and 45% for PTS). In-stent re-thrombosis was the most common type of recurrent VTE, whereas contralateral DVT and PE were rare. One-year recurrent VTE incidence was 25% increasing to 32% at three years. Thrombophilia and LIVCS were not associated with recurrent VTE after multivariate analysis. Most recurrent VTE occurred within the first year (67%), when most patients (87%) used anticoagulation therapy. Possible reasons are non-compliance, sub-therapeutic INR range, or insufficient inflow.

The study's anticoagulant management did not affect patency rates compared with other cohorts.²⁰ Anticoagulants were stopped in 22 patients (28%) after physician approval and/or bleeding complications; one patient stopped against medical advice. Five patients restarted anticoagulants after recurrent VTE. Most patients had primary stent patency with adequate inflow. All patients presented with or after provoked DVT. Therefore, recurrent VTE was deemed unlikely. Patency was successfully restored in all five patients. One had a concomitant contralateral DVT, a complication (0-15.6%) associated with stenting across the ilio caval confluence.²⁴

Whether LIVCS counts as a provoking factor is unclear, but its role in VTE has previously been emphasized. Increased CIV compression severity has been associated with decreased PE risk, with more PEs in right sided DVT.²⁵ Iliac DVT is more frequently left sided than infra-inguinal DVT, with a ratio of left to right sided DVT of 2.4/1 vs 1.3/1, respectively.²⁶ Longer median anticoagulation duration for provoked compared with unprovoked DVT probably reflects decisions to stop anticoagulation after successful resolution of venous compression in unprovoked DVT with LIVCS. That LIVCS currently may be incorrectly considered "unprovoked", is suggested by the high representation of LIVCS in unprovoked DVT (71%). Of 12 patients with unprovoked DVT and LIVCS, five (42%) stopped anticoagulants after a median treatment duration of 54 weeks (IQR 38, 91), with median cessation time of 42 weeks (IQR 6, 243). All maintained patent stents,

without recurrent VTE. Whether LIVCS induces stasis and thereby contributes to Virchow triad and thrombus formation should be investigated. Cessation of anticoagulants after successful venous stenting for LIVCS (and whether LIVCS counts as a provoking factor) also requires further research. Future studies could prospectively measure LIVCS uniformly in all patients and investigate protocols for cessation of anticoagulants, especially in DVT patients with LIVCS.

Cessation of anticoagulants was based on physician and patient preference in the lack of a strict protocol. Indefinite anticoagulation therapy was recommended for unprovoked DVT without LIVCS, according to recent VTE guidelines.¹⁵ During the last decade of the cohort, type and duration of anticoagulation therapy were discussed by multidisciplinary teams. Cessation was considered after at least 12 months for I) provoked DVT with primary stent patency and resolved provoking factor; and II) unprovoked DVT with LIVCS resolved, for both under the condition of primary patency and adequate inflow. Several other factors contributed, such as bleeding complications and therapy non-compliance. Reasons for cessation after earlier procedures was not always retrievable.

There is no consensus on the role of thrombophilia for clinical decision-making after venous stenting.¹⁷ A previous study reported a thrombophilia prevalence of 46.9% after venous stenting for unprovoked DVT.²⁷ Another study identified thrombophilia in 50% of the cohort.²⁸ Selection bias might explain the lower thrombophilia incidence in the present study's cohort (32%); thrombophilia was screened in *all* patients for the study purpose. These additional tests yielded five additional patients, while 20 patients were already identified after tests for clinical indications.

The results suggests that thrombophilia may increase recurrent VTE risk, but lost significance after multivariable analysis. Association with thrombophilia was also lacking in a subanalysis of in-stent re-thrombosis (log rank: $p=.070$). Previous re-intervention rates were similar after venous stenting in patients with and without thrombophilia.²⁷ No significant differences were found for first occlusion or reflux between patients with and without thrombophilia after venous stenting for iliofemoral DVT.²⁹ The study's findings support recommendations of the European Society for Vascular Surgery (ESVS) on the management of venous thrombosis (2021): thrombophilia testing is not recommended for patients with provoked DVT (Class III, level C).⁹ This is also underlined by the American Society for Hematology (ASH) guidelines, which discourage thrombophilia testing in most cases.³⁰ Determining whether DVT is unprovoked, or provoked (transient or persistent) is essential to guide clinical decision-making on anticoagulant treatment duration.¹²

This study had several limitations including sample size, single center, retrospective design, various follow up times, unavailable time interval between DVT and PTS development, and lack of central adjudication of the initial thrombus removal and stenting procedure. There was a potential risk of collinearity and overfitting, that we could not be accounted for. These limitations may explain why recurrent VTE risk factors were not identified. The long follow up was a strength of the study, but also carries evolution of clinical treatment strategies, technologies, and experience. Mixed cohort and uncertain classifications were also limitations. Patients with DVT have an active inflammatory process, patients with PTS have chronic fibrosis disease, which have different patency outcomes.³¹ Presence of LIVCS and DVT classification were based on retrospective data. Compliance with anticoagulants could not be verified and there was a possibility for under-reporting asymptomatic PE. Lastly, results of thrombophilia tests were unblinded for treating physicians and may have affected treatment decisions (bias by indication).

CONCLUSION

Recurrent VTE occurred in 38% patients (32% DVT; 45% PTS) almost always (93%) in-stent re-thrombosis. Recurrent VTE was 25% after cessation of anticoagulation: stent patency was restored in all these patients. Thrombophilia and LIVCS were not associated with recurrent VTE after multivariable analysis. This study serves as a step up to optimisation of anticoagulant therapy and encourages investigation of prospective protocols for (cessation of) anticoagulant therapy after venous stenting.

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PART III

LONG-TERM RESULTS AFTER VENOUS STENTING FOR ACUTE DEEP VEIN THROMBOSIS AND POST-THROMBOTIC SYNDROME



3A



Long Term Follow Up, Causes for Re-intervention, and Consequences for Surveillance After Stenting for Proximal Deep Vein Obstruction

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ABSTRACT

OBJECTIVE

Venous stenting is performed increasingly for acute deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS) with good short term patency results, but long term data are scarce. The purpose of this study was to evaluate long term outcome of stenting for acute DVT and PTS and to study causes of re-intervention.

METHODS

All patients stented for acute DVT and PTS between May 2006 and November 2021 were included retrospectively in this single centre cohort study. Patency was studied by duplex ultrasound (DUS) or computed tomography. The primary endpoint was stent patency. Re-intervention free survival was calculated using Kaplan–Meier methods. Secondary endpoints were causes of re-intervention, using the Pouncey classification system (2022). Binary logistic regression was used to calculate odds ratios for predictors of re-intervention.

RESULTS

A total of 114 patients were included, with 129 limbs involved (acute DVT $n = 53$; 41%), PTS $n = 76$; 59%). Median follow up was 2.3 years (interquartile range [IQR] 2.3) for acute DVT and 5.2 years (IQR 7.1) for PTS. Primary patency, secondary patency, and permanent occlusion were 73.5%, 98.1%, and 1.9% for acute DVT, and 63.2%, 92.1%, and 7.9% for PTS limbs. Overall, 41 limbs underwent at least one re-intervention: 14 in the acute DVT group and 27 for PTS. Most re-interventions (82.9%) were performed within the first year after stenting. Missed inflow, insufficient flow, and thrombosis despite anticoagulation were the most common causes of re-intervention. The strongest predictor for re-intervention for PTS was inflow disease (odd ratio 3.57, 95% confidence interval 1.26 – 10.13, $p = .017$).

CONCLUSION

Long term patency of deep venous stenting is good. Re-interventions are typically performed in the first year and are potentially preventable by improving the procedure and patient selection. Since secondary patency rates are excellent, selected patients may be considered for discharge from long term surveillance.

INTRODUCTION

Acute iliofemoral deep vein thrombosis (DVT) is usually more symptomatic than a distal DVT and frequently leads to post-thrombotic syndrome (PTS).^{1,2} Various symptoms and signs may arise with PTS, such as heaviness, cramps, oedema, venous claudication, skin changes, and venous ulceration.³ Thrombus removal strategies, often combined with venous stenting, may lower the risk of PTS in selected patients with acute iliofemoral DVT.⁴⁻⁸ Venous stents can also restore patency and relieve symptoms of outflow obstruction in PTS.⁹⁻¹²

The European Society for Vascular Surgery (ESVS) guidelines on venous thrombosis provide a class IIA, level A recommendation: In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered.⁷ The ESVS guidelines on the management of chronic venous disease provide a class IIA, level B recommendation: For patients with iliac vein outflow obstruction and severe symptoms/signs, endovascular treatment should be considered, as the first choice treatment.¹³

Patency outcomes are overall promising after deep venous stenting, but less is known about long term patency.^{8,9,14} Patency seems worse for stents across the inguinal ligament, stents with poor inflow, early designed non-dedicated venous stents, and for PTS compared with those treated for non-thrombotic iliac vein lesions (NIVLs), but current evidence is scarce with conflicting outcomes.^{13,15,16,17} A better understanding of long term patency and causes of re-intervention could help to improve patency, patient selection and follow up strategies.

Main study aim

The aim was to evaluate long term outcome of stenting for acute DVT and PTS and to study causes of re-intervention.

MATERIALS AND METHODS

Cohort

This cohort study is reported following the STROBE guidelines.¹⁸ Patients stented between May 2006 and November 2021 for acute DVT or obstructive PTS at an academic hospital were included retrospectively. Endovenous treatment for acute DVT was introduced later at the institution for PTS. Patency data were collected until 1 February 2022. Venous stents in patients with an active malignancy in a palliative setting were excluded.

Patients and procedural characteristics were retrospectively extracted from medical records. Patients were still attending the outpatient clinic or had been discharged from follow up. Discharged patients were prospectively asked for informed consent to examine stent patency using duplex ultrasound (DUS). Patients were excluded from the analyses if patency follow up was shorter than the 12 week follow up (except for permanent stent occlusion). The local Medical Ethics Committee approved this study (MEC-2020-0429).

Procedure

All patients had at least iliac, iliofemoral, and or caval obstruction. Acute DVT was diagnosed with DUS and or computed tomography (CT). Thrombolysis or percutaneous thrombectomy was performed to relieve significant acute leg swelling and pain. At least one venous stent was placed at the end of these procedures if a significant stenosis remained ($> 50\%$) on phlebography or intravascular ultrasound (IVUS). Venous stenting was also performed for proximal venous outflow obstruction due to moderate or severe PTS (Villalta scale ≥ 10),³ or severe venous claudication, at least one year after acute DVT.

Inflow was scored with phlebography and or IVUS for all patients during the procedure (for acute DVT after clot removal). Pre-procedural inflow was scored using DUS and magnetic resonance imaging (MRI) for PTS patients. To be considered sufficient, the femoral vein (FV) and deep femoral vein (DFV) had to be patent. Minimal trabeculation of the common femoral vein (CFV) was allowed, since endophlebectomy was not performed at the treating centre. From 2017 onwards, IVUS was used during all procedures. Patients were treated with oral or subcutaneous therapeutic anticoagulants immediately after stent placement, usually low molecular weight heparin and switched to vitamin K antagonists after two weeks.

Post-procedure follow up

Patency was evaluated by DUS one day after stenting and thereafter repeated at the outpatient clinic by a trained dermatologist or vascular surgeon, at two, six, and 12 weeks, six months, and annually thereafter. The same follow up protocol was used after re-intervention. Additional CT imaging was performed if patency was unclear on DUS. Type and duration of anticoagulation were discussed with a haematologist. Anticoagulant therapy was at least 12 months and extended on the basis of individual needs. Patients with unprovoked DVT, persistent provoking factor for DVT, and or recurrent DVT were candidates for indefinite anticoagulant treatment. Stopping anticoagulants after 12 months was considered if a clear transient provoking factor for DVT was present and stents were primarily patent.

Re-intervention

Re-interventions were performed for thrombosed stents or significant stenosis (> 50%) on DUS, either during routine follow up or when patients reported complaints, after confirmation on CT imaging, phlebography, and or IVUS. Re-intervention causes were investigated and discussed between the interventional radiologist and vascular surgeon. Missed inflow and outflow, or stent fracture, were covered with a stent (most distal part possible being the CFV). The inflow from the FV and DFV was visualised. Anticoagulant therapy was discussed with the haematologist. Re-interventions included in stent stenting, stent extension, percutaneous transluminal angioplasty, and or thrombolysis. Three authors (J.B., A.M., M.R.) retrospectively addressed the causes of re-intervention after stenting for acute DVT and PTS. Re-interventions were classified using the system of Pouncey et al.¹⁹ Re-interventions were classified as technical (type 1), flow related (type 2), haematological (type 3), or multifactorial (type 4), after reaching consensus. Type 2 was scored using per-procedural phlebography and or IVUS images, examining pre-procedural DUS/MRI images (for PTS) or post-DUS images (for DVT) if inflow was unclear from phlebography. Technical causes for re-intervention were missed inflow due to inadequate stenting of existing venous lesions (1B), missed outflow due to inadequate venous stenting proximally (1C), or device failure (1D: stent fracture [F], compression [C], or migration [M]). Haematological causes for re-intervention were inadequate anticoagulant therapy (3A), or thrombosis despite anticoagulation (3B). Patients without venous stents (1A) were not included. The re-intervention classification was shown as count with percentage and counted multiple times if multifactorial.

Outcomes

The primary endpoint was long term stent patency, described using re-intervention free survival. Secondary endpoints were re-intervention causes, according to Pouncey et al.¹⁹ Primary stent patency was defined as a patent stent without re-intervention (minimal thrombosis or trabeculation was accepted if venous flow was sufficient on imaging); secondary patency as a patent stent (eventually with minimal thrombosis or trabeculation), after one or more re-interventions; permanent occlusion as an occluded stent, without further options for recanalisation.

Definitions – characteristics

Stents across the inguinal ligament extended into the CFV. Stent length was summed for all stents used on each side, without correcting for overlap. Patients with bilateral stents were included twice, once for the left and once for the right side as each leg was analysed separately. Dedicated venous stents were used for most procedures; non-dedicated stents were also used but only before

2017. Since 2017, a multidisciplinary team (MDT) has been introduced to standardise dedicated venous stenting, use of IVUS, and post-procedural follow up. Complications within 30 days included all bleeding and thrombotic events after the primary procedure and were scored using the Clavien–Dindo classification: I = deviation of normal post-operative course without the need for treatment; II = requiring pharmacological treatment, III = requiring surgical, endoscopic, or radiological intervention; IV = life threatening complication requiring intensive care management; V = mortality.²⁰

Statistical analysis

Categorical variables are presented as count with percentage and compared using the Pearson's chi-square or Fisher's exact test. Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). The Shapiro–Wilks test was used to test the sampling distribution, the Student t test was used for normally distributed data, and the Mann–Whitney U test for skewed data. Confidence intervals (CI) of 95% were used and statistically significant if $p < .05$. Event free survival for re-intervention was studied by Kaplan–Meier methods and compared using the log rank test. Binary logistic regression was used to calculate odds ratios.

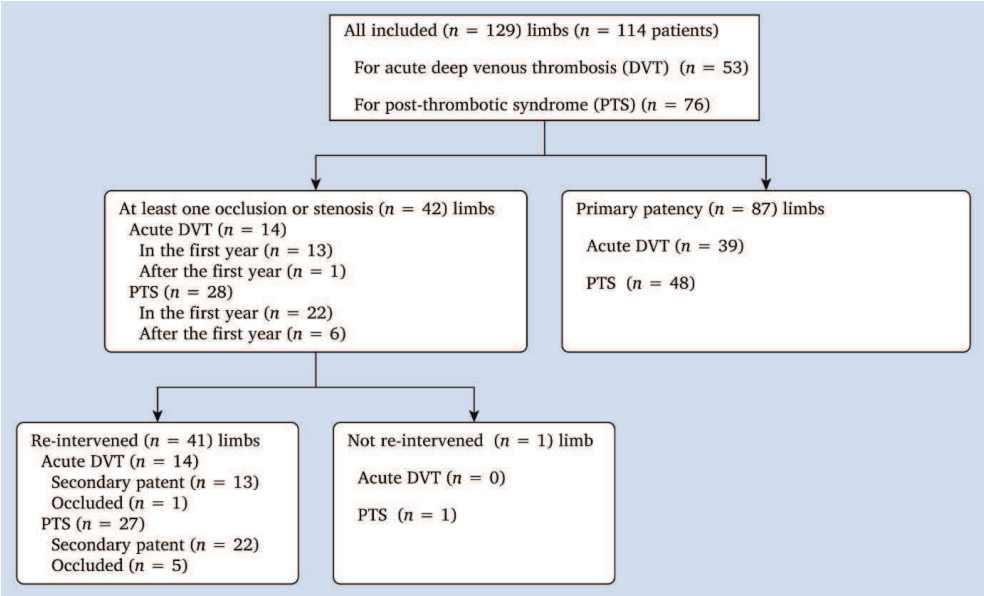
Missing variables were excluded from the analysis. For stent patency, at the last observation carried forward method was used to account for missing data, which was applied to seven patients (5.4%). Patency data were available for all others. Missing data were 6.2% for length of stents and 3.1% for inflow disease.

RESULTS

Study cohort

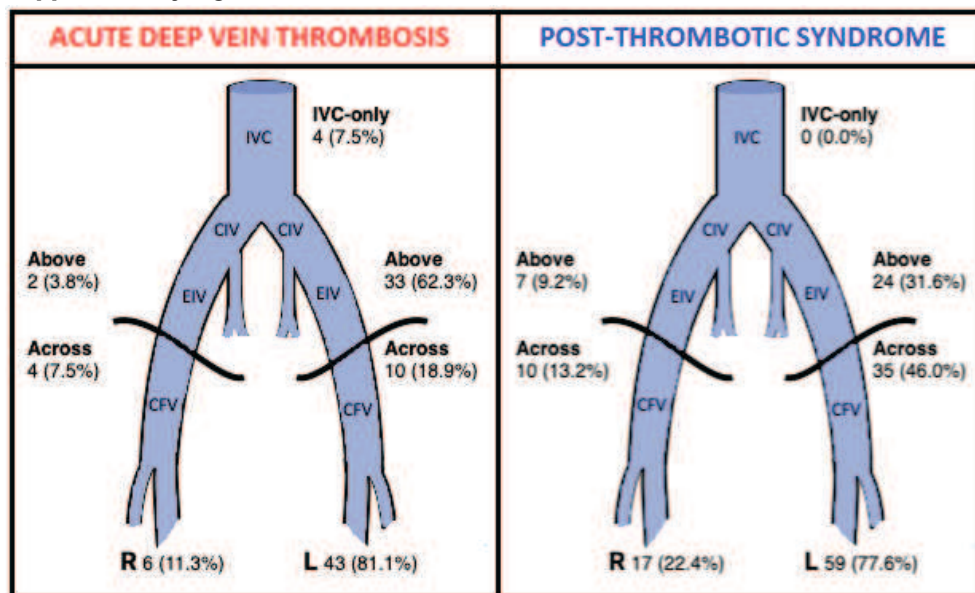
A total of 129 limbs in 114 patients were included: 53 (41%) stented for acute DVT and 76 (59%) for PTS, after excluding three patients because of < 12 weeks DUS follow up (too recent procedure to attend 12 weeks follow up visit yet). Included patients, re-interventions and patency are shown in [Figure 1](#).

Figure 1. Flowchart patency of venous stenting for acute deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS).



Patient and procedure characteristics

Most acute DVT and PTS stents were placed on the left side (81.1% and 77.6% respectively) and four patients were only stented in the inferior vena cava (Supplementary Figure S1). Patients stented for PTS were significantly older (mean 46 vs. 42 years, $p = .17$) and more frequently female (83.3% vs. 62.5%, $p = .012$) compared with acute DVT (Table 1). Stents for PTS were longer, and more often placed across the inguinal ligament (59.2%) compared with stents for acute DVT (26.4%, $p < .001$). Median DUS follow up was shorter for acute DVT (2.3 years; IQR 2.3) than for PTS (5.2 years; IQR 7.1).

Supplementary Figure S1. Localisation of venous stents.**Table 1.** Patient and procedural characteristics for patients with acute deep vein thrombosis or post-thrombotic syndrome at the time of the procedure.

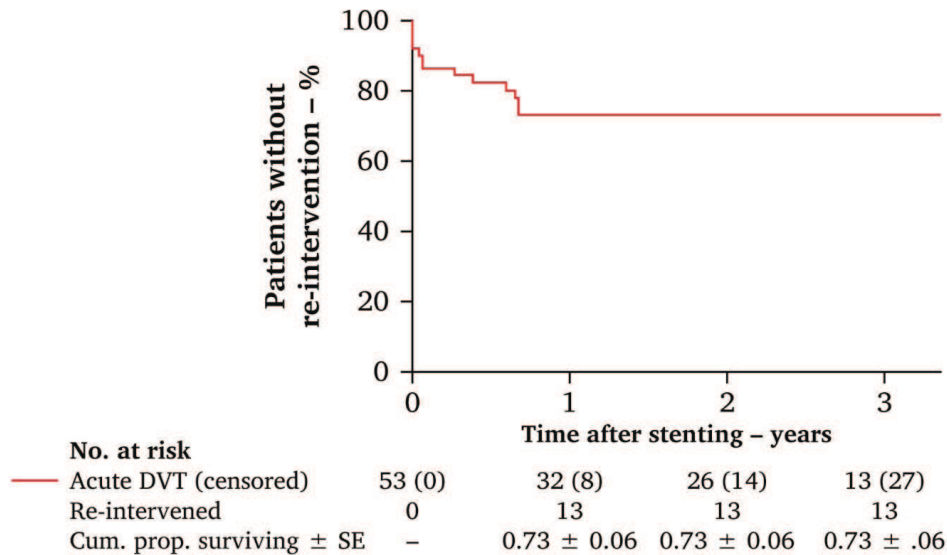
Patients	Acute DVT n= 48	PTS n= 66	p-value
Age, years	42 ± 17.7	46 ± 15.4	.17
Female sex	30 (62.5)	55 (83.3)	.012
Stented Limbs	n= 53	n= 76	
Primary patency	39 (73.5)	48 (63.2)	.21
Secondary patency	52 (98.1)	70 (92.1)	.24
Stent across inguinal ligament	14 (26.4)	45 (59.2)	<.001
Inflow disease FV/DFV *	10 (18.9)	40 (55.6)	<.001
Length of stents, mm*	176 ± 120.1	214 ± 100.6	.019
Follow-up till last duplex, years	2.3 (IQR 2.3)	5.2 (IQR 7.1)	<.001

Data presented as n (%) or mean ± standard deviation or median with interquartile range (IQR); * missing values excluded; FV= Femoral Vein; DFV= Deep Femoral Vein; DVT= Deep Vein Thrombosis; PTS= post-thrombotic syndrome.

Patency and re-intervention free survival

Primary patency, secondary patency, and permanent occlusion were 73.5%, 98.1%, and 1.9% for acute DVT, and 63.2%, 92.1%, and 7.9% for PTS. Re-intervention free survival within three years after stenting for acute DVT is shown in Figure 2. Patency was lost almost exclusively within the first year. Only one stent occluded after three years (therefore not shown in Fig. 2).

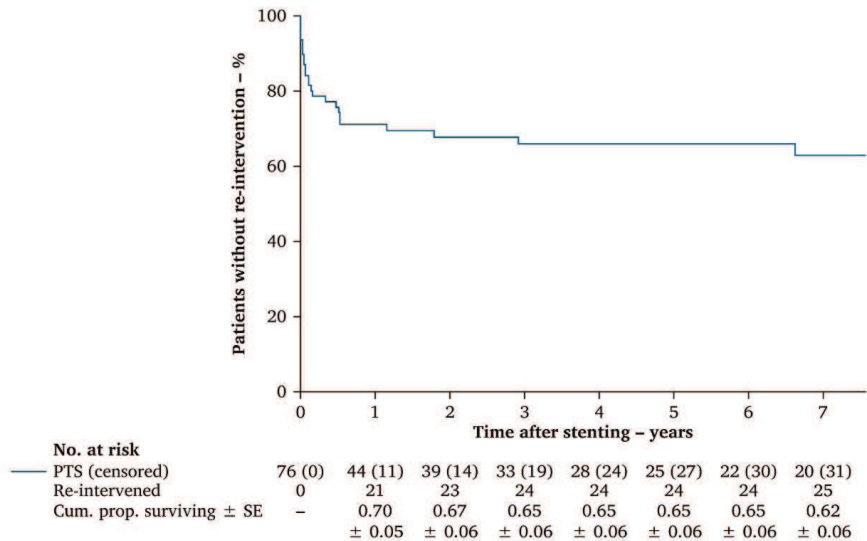
Figure 2. Cumulative Kaplan–Meier estimate of re-intervention free survival after stenting for acute deep vein thrombosis (DVT).



SE = standard error.

Re-intervention free survival within seven years after stenting for PTS is shown in Figure 3. One patient was censored after 11 weeks because of permanent occlusion without re-intervention. Re-interventions also peaked within the first year of follow up for PTS; however, some stents still lost patency thereafter.

Figure 3. Cumulative Kaplan–Meier estimate of re-intervention free survival after stenting for post-thrombotic syndrome (PTS).



SE = standard error.

Re-intervention

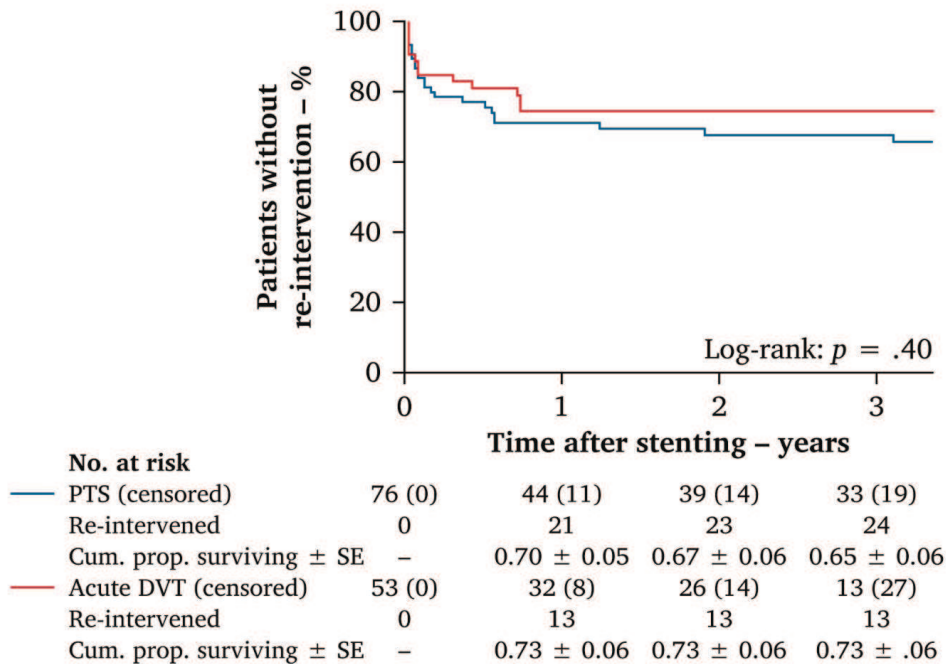
Of all 41 limbs undergoing re-intervention (36 patients) within the whole cohort, 51.2% had one, 26.9% had two, 17.1% had three, 2.4% had four, and 2.4% had five re-interventions. Thirty-four limbs (82.9%) underwent re-intervention within the first year after the primary procedure, of which 20 limbs were within the first 30 days. Classification of re-interventions after the primary procedure is shown in [Table 2](#) for both acute DVT and PTS. For acute DVT, missed inflow (42.9%) and thrombosis despite anticoagulation (50.0%) were the most common cause of re-intervention, while for PTS, these were missed inflow (37.0%) and flow related (33.3%). Multifactorial causes were common in both groups (21.4% for acute DVT and 29.7% for PTS stents) ([Fig. 4](#)). Six of 14 re-interventions for acute DVT had repeat re-intervention: n= 3 classified 1B, n= 2 classified as 1C, and n= 1 classified as 3B. For PTS, 14 of 27 re-interventions were repeat re-interventions: n= 8 classified as 1B, n= 1 classified as 1C, n= 1 classified as 1D, n= 2 classified as 3A, and n= 1 classified as 3B; n= 5 re-interventions were type 4, multifactorial.

Table 2. Classification of etiology of the first re-stenosis or occlusion after stenting for acute deep vein thrombosis or post-thrombotic syndrome.

Failure classification	Etiology	Acute DVT n= 14	PTS n= 27	p-value	OR [95% CI]
<u>Type 1, technical</u>					
1A No stent	Residual disease	n.a.	n.a.	n.a.	n.a.
1B Missed inflow	Inadequate stenting of existing venous lesions: stent not extended distally	6 (42.9)	10 (37.0)	.71	0.78 [0.21-2.92]
1C Missed outflow	Inadequate stenting of existing venous lesions: stent not extended proximally	2 (14.3)	3 (11.1)	.56	0.75 [0.11-5.11]
1D Device failure Fracture (F) Compression (C) Migration (M)	Stent failure can be subcategorized as F, C, or M	C: 1 (7.1)	C: 3 (11.1) M: 1 (3.7)	.44	2.26 [0.23-22.43]
<u>Type 2, Flow</u>	Scarring or occlusion of vessels not amenable to stenting – femoral, profunda, or popliteal vein	1 (7.1)	9 (33.3)	.066	6.50 [0.73-57.83]
<u>Type 3, Hematologic</u>					
3A Dose-related	Noncompliance or sub-therapeutic anticoagulation	0 (0)	4 (14.8)	.17	n.a.
3B Non-dose-related	Thrombosis despite anticoagulation	7 (50.0)	6 (22.2)	.074	0.29 [0.07-1.14]
<u>Type 4, Multifactorial</u>	Mixed etiology	3 (21.4)	8 (29.7)	.25	2.53 [0.46-13.96]
	§ 1B + 2	§ 0	§ 5		
	§ 1B + 3B	§ 2	§ 0		
	§ 1B + 2 + 3B	§ 0	§ 1		
	§ 2 + 3A	§ 0	§ 1		
	§ 2 + 3B	§ 1	§ 0		
	§ 1D-C + 3B	§ 0	§ 1		

Data presented as count (%); Cases with multifactorial classification counted twice; Classification for re-intervention of Pouncey et al. (2022)¹⁹; n.a.= not applicable.

Figure 4. Cumulative Kaplan–Meier estimate of three year re-intervention free survival after stenting for acute deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS).



SE = standard error.

Long term re-interventions

A first re-intervention after one year of primary patency was observed in seven limbs, between one year + eight weeks and nine years + 40 weeks of follow up, shown in [Supplementary Table S2](#). Six limbs underwent re-intervention in female patients with PTS, and one limb in a male patient with acute DVT. Inadequate anticoagulant therapy (type 3A) led to three re-interventions. One re-intervention was required because of thrombosis despite anticoagulation (type 3B). Two re-interventions were required due to inflow related issues (type 1B), while one re-intervention was required due to outflow related issues (type 1C). Among these, one inflow related re-intervention was multifactorial (type 4), as it was also related to flow (type 2). Predictors for re-intervention after stenting for acute DVT and PTS are shown in [Table 3](#). Increased age protected against re-intervention, while inflow disease increased the risk of re-intervention in PTS patients. No significant predictors were identified for re-intervention in acute DVT patients.

Supplementary Table S2. First re-intervention after one year of primary patency (n= 7).

Patient	Follow-up, years + weeks	Classification + Type of re-intervention
Female - Age: 35 - PTS - Right	1 yr + 8 wk	Hematologic, dose-related (3A): Patency restored after PTA for in-stent stenosis after stopping oral anticoagulation (despite a lifelong indication for anticoagulants).
Female - Age: 24 - PTS - Left	1 yr + 41 wk	Hematologic, dose-related (3A): Acute stent thrombosis after stopping oral anticoagulation. Final stent occlusion despite thrombolysis.
Female - Age: 29 - PTS - Bilateral	2 yr + 48 wk (left) 9 yr + 30 wk (left) 6 yr + 33 wk (right)	Missed inflow (1B): 1. Patency restored after distal stent extension towards the CFV. Hematologic, thrombosis despite anticoagulation (3B) 2. Patency restored after PTA and bilateral stent-in-stent placement at the iliac confluence into the IVC, because of in-stent stenosis. Patient known with anti-phospholipid Syndrome.
Male - Age: 54 - DVT - Left	3 yr + 20 wk	Missed outflow (1C): Insufficient stent during the primary procedure (performed at another institution). Patency restored after stent extension across the May-Thurner point into the IVC.
Female - Age: 36 - PTS - Left	8 yr + 18 wk	Multifactorial (4): missed inflow (1B) + flow (2). Partial stent occlusion in the CIV with extensive EIV trabeculation. Patency restored after PTA and distal stent extension
Female - Age: 27 - PTS - Left	9 yr + 40 wk	Hematologic, dose-related (3A): anticoagulants stopped. Patency restored after stent-in-stent procedure.

Age (years) at primary procedure; PTA= Percutaneous Transluminal Angioplasty;
CFV= Common Femoral Vein; DVT: Deep Vein Thrombosis; PTS= Post-Thrombotic Syndrome;
EIV= External Iliac Vein; CIV= Common Iliac Vein; IVC= Inferior Vena Cava.

Table 3. Univariable binary logistic regression for re-intervention.

Variable	Acute Deep Vein Thrombosis n= 53 limbs			Post-Thrombotic Syndrome n= 76 limbs		
	OR	95% CI	p-value	OR	95% CI	p-value
Age – years per decade	0.97	0.67-1.39	.85	0.68	0.48-0.96	.029
Female sex	0.47	0.14-1.62	.23	3.53	0.92-13.55	.066
Stent across inguinal ligament	1.85	0.49-6.95	.36	2.74	0.98-7.66	.054
Inflow disease FV/DFV	2.20	0.52-9.38	.29	3.57	1.26-10.13	.017
Stent length – above median	3.33	0.79-14.16	.10	0.64	0.25-1.67	.36
Since start MDT	1.44	0.34-6.17	.62	0.33	0.11-1.02	.053

FV= Femoral Vein; DFV= Deep Femoral Vein; MDT= Multidisciplinary Team; median stent length 120 mm for acute DVT, n= 4 missing, and 230 mm for PTS, n= 4 missing; inflow disease n=4 missing for PTS.

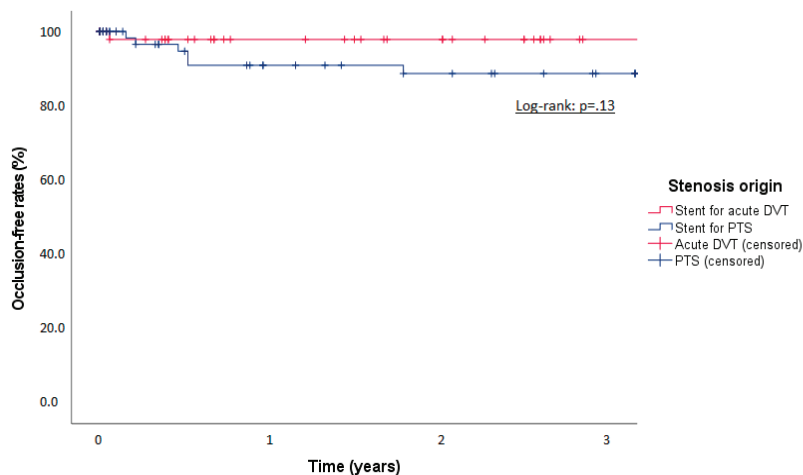
Permanent occlusion

Seven limbs (six patients) remained occluded after a median DUS follow up of 11 weeks (IQR 24), shown in Supplementary [Table S3](#). Patients were between 14 and 49 years old at the time of the primary procedure. The permanent occlusion free survival after stenting for PTS and acute DVT is shown in Supplementary [Figure S4](#). One occlusion occurred after stenting for acute DVT, the remaining six after stenting for PTS. Three (50%) limbs were occluded within the first week. Causes of re-intervention were multifactorial (n= 4), missed inflow (n= 1), and inadequate anticoagulant therapy (n= 1). Missed inflow was a common cause of re-intervention (n= 4). One patient did not undergo re-intervention because of pre-existing poor inflow.

Supplementary Table S3. Permanent occlusion.

Patient	Time to last open	Type of re-intervention
Male - Age: 18 - DVT - Left	0 weeks	Multifactorial (4): missed inflow (1B) + hematologic, non-dose-related (3B). In-stent-thrombosis was not resolved, despite thrombolysis. Patient with anti-thrombin-3 deficiency and factor II variance.
Female - Age: 49 - PTS - Bilateral	0 weeks (2x)	Left: Multifactorial (4): missed inflow (1B) + flow (2). Inadequate inflow from the left EIV and distal veins. Right: Missed inflow (1B). Inadequate inflow from the right EIV, but good inflow from DFV and FV.
Female - Age: 25 - PTS - Left	11 weeks	Multifactorial (4): device failure, compression (1D) + hematologic, non-dose-related (3B). Patient with anti-phospholipid syndrome. In-stent-thrombosis after 2 PTA's for an in-stent stenosis with DVT extending into the DFV and FV. Thrombolysis was unsuccessful to re-open the leg or the stent.
Male - Age: 41 - PTS - Left - Bilateral	11 weeks	No re-intervention: classification not applicable. Unilateral occlusion after bilateral stenting without any subsequent re-intervention because of pre-existent poor stent inflow.
Female - Age: 14 - PTS - Left	24 weeks	Multifactorial (4): missed inflow (1B) + flow (2). PTA for in-stent stenosis followed by stent extension into the FV. Soon after that in-stent-thrombosis. Poor inflow. Unsuccessful thrombolysis
Female - Age: 24 - PTS - Left	3 years + 7 weeks	Hematologic, dose-related (3A): Acute in-stent thrombosis after stopping anticoagulation due to vaginal blood loss during pregnancy. No new intervention performed, since 2 previous attempts with thrombolysis were unsuccessful.

Age (years) at primary procedure; DVT= Deep Vein Thrombosis; PTS: post-thrombotic syndrome; IVC= Inferior Vena Cava; CIV= Common Femoral Vein; EIV= External Iliac Vein; CFV= Common Femoral Vein; DFV= deep femoral vein; FV= femoral vein; PTA= Percutaneous Transluminal Angiography

Supplementary Figure S4. Permanent occlusion-free survival within 3 years.

No. at risk for debut for permanent occlusion

	Baseline	1 year	2 years	3 years
• PTS (censored)	76 (0)	60 (11)	56 (15)	49 (22)
Permanent occlusion	0	5	5	5
Cum. prop. surviving ± standard error	-	0.92 ± 0.03	0.90 ± 0.04	0.90 ± 0.04
• Acute DVT (censored)	53 (0)	41 (11)	29 (23)	14 (38)
Permanent occlusion	0	1	1	1
Cum. prop. surviving ± standard error	-	0.98 ± 0.02	0.98 ± 0.02	0.98 ± 0.02

Bleeding and thrombotic events (< 30 days)

Bleeding events were reported after 13 initial procedures (10.1%): seven (13.2%) after stenting for acute DVT and six (7.9%) after stenting for PTS. Bleeding after stenting for acute DVT was presumably related to thrombolysis ($n = 4$), including haematuria, haemoptysis, and epistaxis; or was possibly unrelated to thrombolysis ($n = 3$), including haematoma at the puncture site. Most were minor bleeding without the need for any treatment, including haematuria or haematoma: Clavien–Dindo I ($n = 10$). Fluid and or blood transfusion was required for three PTS patients: Clavien–Dindo II ($n = 3$). Thrombotic events were reported after five (9.4%) acute DVTs, and eight (10.5%) PTS procedures. These were mostly in stent thromboses requiring re-intervention: Clavien–Dindo IIIA ($n = 13$). One patient had an in stent thrombosis extending to the distal veins. The stent, the FV, and the DFV remained occluded despite thrombolysis. One acute DVT patient had a superficial and popliteal DVT after the procedure, but the stent in the common iliac vein remained patent: Clavien–Dindo I ($n = 1$). Major thrombotic events, including symptomatic pulmonary embolism or ischaemic cerebrovascular accident, were not seen within the first 30 days.

Multidisciplinary team

The number of acute DVT procedures has significantly increased since the introduction of a multidisciplinary team (21.5% of all procedures before 2017, 60.9% after 2017). Re-intervention rates did not significantly decrease (38.5% vs. 25.0% respectively, $p = .10$).

DISCUSSION

This study reports long term DUS follow up after venous stenting with re-intervention free survival of up to three years for acute DVT and up to seven years for PTS. Re-interventions and permanent occlusion typically occur in the first year after stenting. They seem avoidable by improving procedural techniques (missed inflow) and patient selection (poor inflow or haematological causes).

For acute DVT, missed inflow and thrombosis despite anticoagulation were the most common re-intervention causes. For PTS, these were mainly missed inflow and flow related. The importance of inflow in PTS patients was again emphasised in a binary logistic regression for re-intervention. Improved technical skills (using IVUS to prevent missed inflow) and better patient selection (pre-operative selection of sufficient inflow and identification of haematological disorders) may have avoided these re-interventions.

Recent ESVS guidelines recommend endovenous techniques for selected symptomatic patients with iliofemoral obstruction for both PTS and acute DVT patients.^{7,13} It remains unclear whether endovenous treatment should always be performed for acute DVT, or if patients should be closely monitored and only treated when PTS develops to prevent over treatment. Stents placed for PTS were longer and more often crossed the inguinal ligament than stents for acute DVT. This may suggest that early clot removal reduces thrombus load, optimises inflow, and limits the stented area. Of course, acute DVT and PTS patients in the present study were different subjects, therefore this hypothesis could not be tested. Timing of treatment should be addressed in future (randomised) studies. Ultimately these studies should find the right balance between over treatment, re-intervention risk, and PTS prevention.

Permanent occlusion almost exclusively occurred within the first weeks after the primary procedure. This finding is in line with findings that permanent occlusion occurs soon after the procedure after a median follow up of two months.²¹ The present study adds that causes of permanent stent occlusion were multifactorial, with missed inflow as a common component. Better understanding of

potential risk factors for re-intervention should optimise acute DVT and PTS treatment and improve future patient selection.

Primary and secondary stent patency of 87% and 89% for acute DVT, and 79% and 94% for PTS are reported in the literature.¹⁶ Primary stent patency was lower in the present study, but secondary patency evenly high in the long term. Learning curve, different patient selection, and different post-procedural protocols might explain the lower primary patency. Short term re-intervention peak after venous stenting for acute DVT and PTS have been described before.²²

This study has several limitations, including the inability of conducting a valid correction for potential confounders in a multivariable analysis due to small sample sizes. The mixed cohort spanning over 15 years has presumably introduced heterogeneity in diagnostics, treatment, and follow up. Therefore, cautious interpretation of the findings is recommended while awaiting prospective long term data from large cohorts. Despite the retrospective study design, it is unlikely that the primary outcome of patency was biased since it was measured objectively by DUS or other imaging modalities. The long DUS follow up, specifically for PTS, is unique and is a study strength. With longer follow up, more re-interventions could be needed, which may be especially true for acute DVT. Asymptomatic patients with patent stents were sometimes discharged from follow up. These patients were asked to return for a recent DUS examination, which minimized the loss to follow up and limited the risk of selection bias. All seven patients allocated using the last observation carried forward (no recent DUS follow up) had patent venous stents after a follow up of more than one year. It is unlikely that misclassification bias was induced, since the discharged patients did not return with complaints. However, some causes for re-intervention might have been misclassified. Thrombosis despite anticoagulation is the only remaining option if inadequate anticoagulant therapy, flow and stent related causes are absent. Therefore, this classification type may rather be seen as an idiopathic cause for some patients. It is suggested that an idiopathic cause of re-intervention should be added to the classification system to improve its accuracy.¹⁹

CONCLUSION

Long term patency of deep venous stenting is good. Re-interventions are typically needed within the first year due to missed inflow, insufficient flow, and thrombosis despite anticoagulation, which are all potentially preventable by better patient selection and improved technical skills. A more thorough understanding of how to identify the perfect stent landing zone and to correctly score inflow will improve outcomes for future deep venous procedures. Since occlusion is rare after one year of primary patency, it may be possible to discharge patients from long term surveillance if they have required no re-intervention, have good inflow at the end of the primary procedure, and remain on anticoagulation.

3A

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Deep Venous Intervention: The Need For Further Investigation

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LETTER TO THE EDITOR

We thank Drs Chen, Jiang, and Li for their great interest in our paper and appreciate the discussion about the results.¹

First, we acknowledge that there are inconsistent data presented in the second paragraph of the results and Table 1.² Age and sex were initially reported per stented limb, but were deemed more appropriately reported per patient. In Table 1, age and sex are therefore presented per patient, while the data in the results section are presented per stented limb.² We regret that this was not adjusted. Fortunately, all analyses were performed using the data presented in Table 1. Therefore, our outcomes and conclusions are correctly presented in the manuscript.

We understand the concerns regarding the non-significant difference in 3 year re-intervention free survival between acute deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS) patients ($p = .40$).² We agree this may have resulted from the small sample size or the long inclusion period. Patient selection might also have played a role. The study that the authors refer to, however, also did not find a significant difference in primary patency between acute DVT (reference) and PTS patients (hazard ratio 1.80, 95% confidence interval 0.89 – 3.64).³

The aim of our study was not to identify the optimal timing of deep venous interventions, for which a randomised controlled trial would be necessary. The retrospective design of our study, and the fact that acute DVT and PTS patients were different individuals, did not allow us to predict whether re-intervention rates would have been different after immediate treatment compared with postponed intervention. Therefore, we did not draw conclusions from the findings in Figure 4,² but instead focused on risk factors for re-interventions and the timeframe in which they occur. We agree that this topic should be addressed in future (randomised) studies.

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4A



Quality of Life After Early Clot Removal for Acute Iliofemoral Deep Vein Thrombosis

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Thrombosis. EJVES Vascular Forum. 2024 Jan;61:44-49. doi: 10.1016/j.ejvsvf.2023.12.004**

ABSTRACT

OBJECTIVE

To evaluate patient reported outcome measures after early clot removal for acute deep vein thrombosis (DVT), using the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and the Short Form Health Survey (SF-36).

METHODS

Cross sectional design. Patients who underwent early clot removal between June 2012 and November 2021 were asked to complete the two questionnaires once. Lower CIVIQ-20 and higher SF-36 scores indicate better quality of life (QoL). Primary endpoints were the median scores. The one sample Wilcoxon signed rank test was used to compare SF-36 physical and mental component summary (PCS and MCS) to the normative and CIVIQ-20 to the minimum. Secondary, non-parametric independent t test or Fisher's exact test examined how age, sex, body mass index, stent placement, re-intervention, and time of questionnaire completion related to QoL. Multivariable linear regression tested whether various variables were associated with QoL.

RESULTS

The response rate was 73.5% (n= 39). Median time of questionnaire completion was 1.8 years (interquartile range [IQR] 3.1) after clot removal. The median CIVIQ-20 of 29.0 (IQR 28.0) was slightly higher than the minimum value 20.0 ($p < .001$). The median PCS (50.5, IQR 16.6) and median MCS (50.2, IQR 14.2) did not differ from the normative of 50.0. However, wide IQRs indicated impairments for a subgroup of patients. None of the tested variables affected QoL except for the finding that re-interventions had a significantly negative impact on the SF-36 MCS (standardised β coefficient of -0.4, $p = .030$).

CONCLUSION

Overall patient reported outcome measures were satisfactory after early clot removal, but impaired physical and mental functioning levels were present in a subgroup of patients. Re-interventions were found to have a negative impact on mental QoL. This finding was independent of time that had passed between the procedure and questionnaire completion. This study emphasises that mental functioning deserves attention, besides the widely recognised physical consequences after invasive acute iliofemoral DVT treatment.

INTRODUCTION

Acute deep vein thrombosis (DVT) is diagnosed in one or two per 1000 persons annually.¹ Oedema, erythema, and pain in the leg are common features of acute DVT and are more severe if the thrombus extends across the inguinal ligament into the iliac veins. Patients with acute iliofemoral DVT are at higher risk of developing post-thrombotic syndrome (PTS) than patients with acute DVT below the level of the common femoral vein.² Acute DVT has an impact on both physical and mental functioning levels.³ The former often receives attention during treatment and follow up, but the latter is more easily overlooked. Physical and mental functioning levels may be severely impaired within the first month after (non-invasively treated) venous thromboembolism (VTE).⁴ The current guidelines of the European Society for Vascular Surgery (ESVS) recommend endovenous treatment in selected patients with symptomatic acute iliofemoral DVT.⁵ This involves early clot removal using pharmacological thrombolysis, standalone percutaneous mechanical thrombectomy (PMT), and or pharmacological catheter directed thrombolysis (PCDT), often followed by stenting. The goal is prevention of PTS and limb salvage in case of phlegmasia cerulea dolens. Although early clot removal has been shown to reduce the risk of PTS,⁵ it may not always improve quality of life (QoL) compared with conservative treatment.⁶ Early clot removal might even serve as an (temporary) extra stressor, because of its invasive character. This cross sectional study evaluated physical and mental QoL after early clot removal for acute iliofemoral DVT, using the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and the Short Form Health Survey (SF-36), and searched for risk factors affecting QoL outcome.

4A

MATERIALS AND METHODS

Cohort

Patients who underwent early clot removal for acute iliofemoral and or ilio caval DVT were screened retrospectively from the hospital's first procedure in June 2012 until November 2021. Patients with inadequate understanding of the Dutch language, cognitive impairment, or who were impossible to invite due to death or living abroad were excluded. Eligible patients were asked for informed consent to complete two questionnaires: the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and the Short Form Health Survey (SF-36). Patients with informed consent and completed questionnaires were included. The questionnaires were completed in a cross sectional design (3 months after the primary procedure), meaning that the time after the procedure varied for all patients. Non-responders and patients with incomplete questionnaires were con-

tacted once again and excluded if no response was sent back after a minimum interval of three months. This study was approved by the local medical ethics board (MEC-2020-0429). The following baseline characteristics were collected retrospectively from medical records: age (in years at time of completing the questionnaire), sex, body mass index (BMI) measured during admission for the intervention, previous diagnosis of diabetes mellitus (DM), peripheral arterial occlusive disease (PAOD), and smoking (either current or former). The current study prospectively recorded venous (stent) patency as a component of a larger study into which it was integrated.⁷ Therefore, patients underwent recent assessment of venous (stent) patency with duplex ultrasound (DUS) or computed tomography (CT). Recent venous (stent) patency assessment was missing for one patient, but this patient has remained free of complaints and or reintervention to date. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to ensure high quality presentation of the study.⁸

Early clot removal

All included patients underwent early clot removal using pharmacological thrombolysis, standalone PMT, and or PCDT, followed by venous stenting if a >50% stenosis was detected by venography and or intravascular ultrasound. Re-intervention was performed in stent thrombosis cases, stenosis, and or device failure (such as stent fracture). Re-interventions included pharmacological thrombolysis, PMT, PCDT, percutaneous transluminal angioplasty, and or additional stent implantation. Permanent occlusion was defined as a vein and or stent occlusion without further options to re-open it.

Quality of life

The CIVIQ-20 is a validated 20 question disease specific questionnaire for chronic venous disease (CVD) that assesses lower limb complaints, impact on daily activities, and mental state.^{9,10} It is divided in four domains: leg pain, physical activity, psychological activity, and social activity. The total score ranges from 20 to 100. A higher score indicates more complaints and a worse QoL. The SF-36 is a 36 question validated survey that assesses generic QoL across eight domains: physical functioning, role limitations due to physical health (role physical), bodily pain, general health, vitality, social functioning, role limitation due to emotional problems (role emotional), and mental health.¹¹ Each domain scores on a scale of 0-100, with a higher score indicating a better QoL, in contrast to the CIVIQ-20 scores. The SF-36 contains a physical and mental component summary (PCS and MCS), which are normative based scores using a mean score of 50 from the general population of the United States as a reference.

Endpoints

Primary endpoints were total median CIVIQ-20 score and SF-36 PCS and MCS after early clot removal with or without venous stenting for acute iliofemoral DVT. Secondary endpoints were risk factors for QoL outcomes.

Statistical analysis

Data were analysed using IBM SPSS software version 28.0.1.0. The questionnaire responses and demographics were analysed using descriptive frequencies. Continuous variables are presented as mean with standard deviation (SD), or median with interquartile range (IQR). Additionally, boxplots were used to visualise the patient reported outcome measures (PROMs). The one sample Wilcoxon signed rank test was used to calculate p values comparing SF-36 component summaries to the normative value of 50.0 of the general population of the United States. For the CIVIQ-20, the one sample Wilcoxon signed rank test was used to compare the outcomes to the minimum value of 20, indicative of no CVD complaints. The Shapiro-Wilk test was used to test whether samples were normally distributed. Multivariable linear regression was used to evaluate whether age, sex, BMI, stent placement, re-intervention, and time between questionnaire completion and the procedure were significantly associated with QoL. A non-parametric independent t test (continuous variables) or Fisher's exact test (categorical variables) was used to assess these parameters between patients within the first quartile (Q1) and last quartile (Q4) of the CIVIQ-20 and SF-36 PCS and MCS. Statistical significance was set at $p < .05$. Missing data were excluded from the analysis.

RESULTS

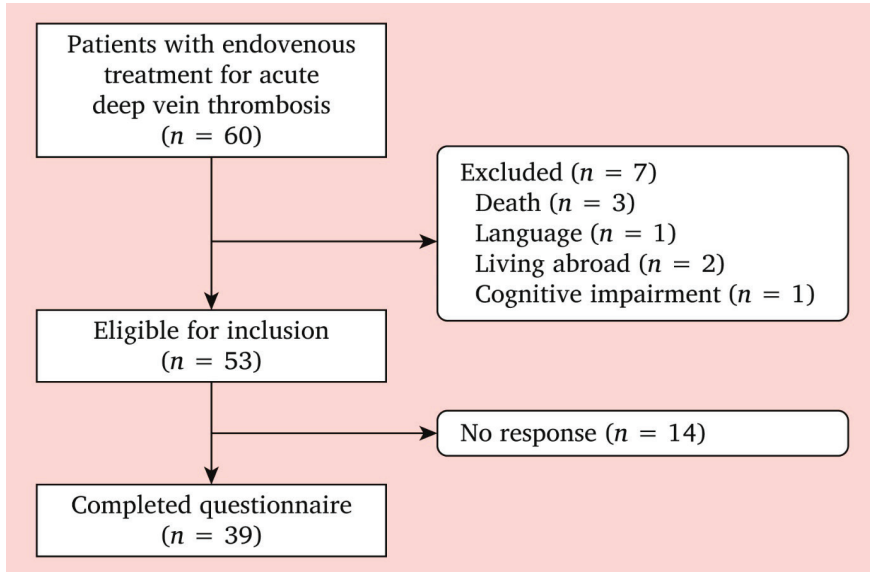
Cohort

Table 1. Patient characteristics.

	Acute DVT (n= 39)
Age, years	44 ± 17
Female	23 (59.0)
Body Mass Index *	25.8 (IQR: 6.6)
Diabetes	1 (2.6)
Peripheral arterial occlusive disease	1 (2.6)
Smoking *	8 (20.5)
Stented	34 (87.2)
Permanent occlusion	1 (2.5)
Time of questionnaire completion, years	1.8 (IQR: 3.1)

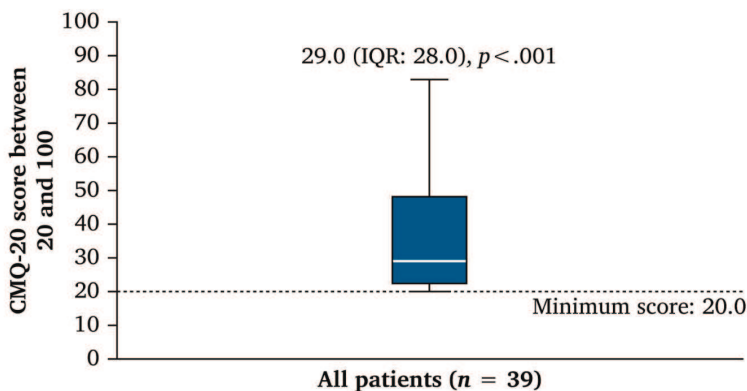
*Categorical variables presented as count (%) and continuous variables as mean ± standard deviation or median with interquartile range (IQR); age and follow-up calculated at time the questionnaire was filled out; *missing values are n=3 for Body Mass Index and n=5 for smoking. Time of questionnaire completion is shown in years between the primary procedure and completion of the questionnaire.*

A total of 60 patients underwent early clot removal for acute iliofemoral DVT, of whom seven were excluded, as shown in [Figure. 1](#). The remaining 53 eligible patients were invited to complete the questionnaires, with a response rate of 73.5% (n= 39). Characteristics of the included patients are shown in [Table 1](#). Patients had a mean age of 44 ± 17 years at time of completing the questionnaires and 59% were female. Early clot removal was followed by venous stenting in the majority of patients (87.2%). The median time between intervention and questionnaire completion was 1.8 years (IQR 3.1). Only one patient had permanent occlusion and venous (stent) patency was preserved in all others, 18.4% underwent re-intervention. Data on BMI and smoking were missing for three and five patients, respectively.

Figure 1. Patient inclusion flowchart.

Chronic Venous Disease Quality of Life Questionnaire

A boxplot with the CIVIQ-20 score is shown in Figure 2. The minimum score of 20 is the best outcome, indicating no complaints and/or disabilities due to CVD. The total cohort had a median score of 29, slightly higher (worse QoL) than the minimum value of 20 ($p < .001$). The interquartile range shows that some patients scored around the minimum score of 20, while the upper border shows the highest score being almost 80.

Figure 2. Total Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) in all included patients.

One sample Wilcoxon signed rank test to compare CIVIQ-20 with the minimum score of 20 indicated by the reference line.

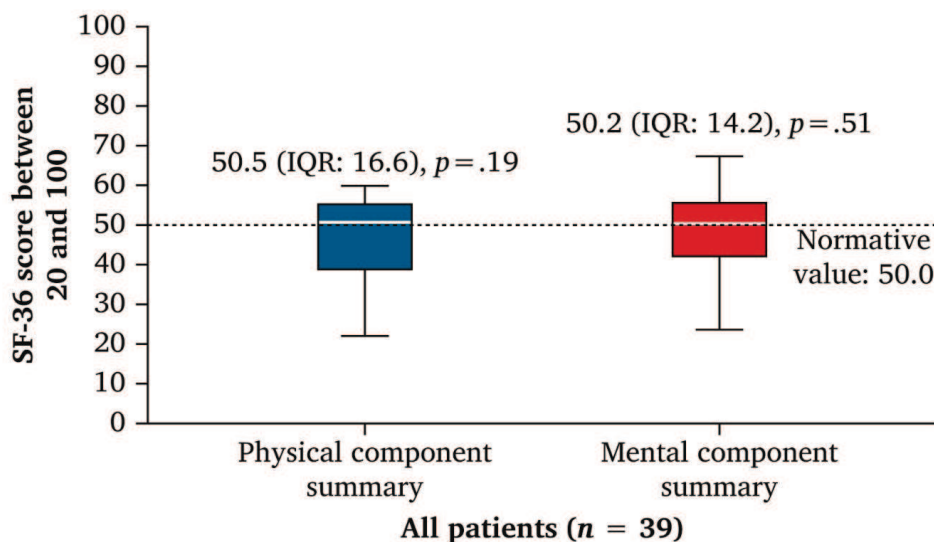
Short Form Health Survey component summary scores

A boxplot for the SF-36 component summaries is shown in [Figure 3](#). The median PCS (50.5, IQR 16.6) and median MCS (50.2, IQR 14.2) were not significantly different from the normative value of 50.0. Meanwhile, the lower and higher borders of the IQRs indicated impaired and better physical and mental functioning levels, respectively, for substantial subgroups of patients.

Subdomains

An extensive overview the SF-36 and CIVIQ-20 complementary subdomains is provided in [Supplementary Table S1](#). Vitality (median 60.0, IQR 35.0) and General Health Perceptions (median 62.0, IQR 35.0) were the lowest (worst) SF-36 domains. The vitality scale includes four questions focused on energy and complaints of fatigue within the past four weeks. General health perceptions include five questions, focusing on the overall rating of current health in general.

Figure 3. Mental and physical component summaries (Short Form Health Survey [SF-36]) in all included patients.



One sample Wilcoxon signed rank test comparing SF-36 scores to the normative value of 50.0 for general population (United States) indicated by the reference line.

Long term quality of life

Multivariable regression analysis to test the effect of several factors on QoL outcomes are shown in [Supplementary Table S2](#). Included variables were age, sex, BMI, stent placement, re-intervention, and time between questionnaire completion and the procedure. None of the variables was associated with QoL except

that re-interventions had a significant negative impact on the SF-36 MCS. For the CIVIQ-20, this was borderline significant (standardised b coefficients of re-intervention: -0.2 for SF-36 PCS, $p = .30$; -0.4 for SF-36 MCS, $p = .030$; and 0.4 for CIVIQ-20, $p = .051$)

Subgroup analysis: PROM within the first and last quartile

Table 2 shows the SF-36 for patients within the first (Q1, worst) and last (Q4, best) quartile and for CIVIQ-20 between the last (Q4, worst) and first (Q1, best) outcomes. Age, sex, BMI, stent placement, re-interventions, and time between questionnaire completion and intervention did not affect QoL outcome.

Table 2. Characteristics of patients within the “worst” and “best” quartile of the SF-36 physical component summary (PCS), SF-36 mental component summary (MCS), and CIVIQ-20.

	SF-36 PCS			SF-36 MCS			CIVIQ-20		
	Q1: (n= 10)	Q4: (n= 10)	p -value	Q1 (n= 10)	Q4: (n= 10)	p -value	Q4 (n= 10)	Q1: (n= 10)	p -value
Age years	40 ± 18	33 ± 16	.28	41 ± 14	45 ± 23	.91	39 ± 18	38 ± 22	.74
Female (%)	6 (60.0)	7 (70.0)	>.99	6 (60.0)	6 (60.0)	>.99	6 (60.0)	5 (50.0)	>.99
Body Mass Index	26.8 ± 6.8 *	26.7 ± 4.1 **	>.99	27.8 ± 5.7	27.3 ± 5.3 *	.66	25.3 ± 6.0 *	26.6 ± 2.6 *	.55
Stented (%)	8 (80.0)	9 (90.0)	>.99	9 (90.0)	10 (100)	>.99	8 (80.0)	9 (90.0)	>.99
Re-inter- vention (%)	3 (30.0)	1 (10.0)	.58	4 (40.0)	2 (20.0)	.63	3 (30.0)	1 (10.0)	.58
Time of question- naire comple- tion years	2.8 ± 2.1	3.4 ± 3.1	.74	2.2 ± 1.7	0.97 ± 1.0	.09	2.1 ± 1.9	2.6 ± 2.9	>.99

Time of questionnaire completion is shown in years between the primary procedure and completion of the questionnaire. PCS= physical component summary. MCS= mental component summary. Data are shown as mean ± standard deviation, or count (%). Q= quartile. n= 1 missing value excluded. ** n=2 missing values excluded.*

Permanent occlusion

Permanent occlusion was found in one male patient aged 22 years at the time of questionnaire completion (3.1 years after the primary procedure). He was stented for acute DVT from the inferior vena cava into the left common femoral vein. His CIVIQ-20 score was 78, SF-36 PCS 29.3, and SF-36 MCS 25.1. Comorbidities included medical history of multiple venous thrombotic events, thrombophilia, and depression.

DISCUSSION

Physical and mental QoL measured by CIVIQ-20 and SF-36 was satisfactory at various timepoints after early clot removal for acute iliofemoral DVT in this cohort of 39 included patients. However, a substantial subgroup experienced physical and or mental disabilities following the procedure. Common complaints were related to fatigue and impaired rating of the patients' own health. This was not explained by a more recent procedure (in terms of longer or shorter time between treatment and questionnaire completion), or by age, sex, BMI, or stenting. However, re-intervention was a significant predictor for lower mental QoL indicated by the SF-36 questionnaire.

Three trials randomised between early clot removal and anticoagulant therapy alone for acute iliofemoral or proximal DVT: ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis), CAVA-trial (Catheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT), and CaVenT-trial (Catheter Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis).¹² Differences in SF-36 were reported from baseline until 24 months for the ATTRACT-cohort.¹² The PCS at one month was higher after early clot removal than anticoagulant therapy alone (difference 3.2, $p = .001$), indicating faster relief of symptoms and signs of acute DVT. No significant differences were found from baseline to other time points, including 24 months of follow up. The MCS improved for both groups over time, but no differences were found between the two treatment strategies from baseline to any assessment, including 24 month follow up. The SF-36 physical health, mental health, and general health domains were reported at 12 months and the final follow up visit for the CAVA cohort.¹³ The intervention group had a (slight) decrease in all domains, indicating a better QoL, but without statistical significance. Statistically significant differences were found between the treatment arms for physical health: additional thrombolysis scored 2.7 points lower, while standard treatment scored 4.4 points higher ($p = .048$), indicating early clot removal to be beneficial for physical functioning. Other PROMs (EQ-5D and

VEINES-QOL/Sym) were reported from the CaVenT cohort, without differences in long term QoL between patients with acute DVT who underwent additional thrombolysis and who received standard treatment.¹⁴ However, it is important to note the heterogeneity between studies in selection criteria (e.g., inclusion of femoropopliteal DVT), treatment techniques, and questionnaires used.

In the present study, QoL was overall satisfactory after early clot removal in iliofemoral DVT patients, but impaired in a subgroup. Assessing QoL is the only way to identify these patients in future clinical practice and should be part of routine follow up, even if patients have a patent iliofemoral vein with or without a stent. Awareness of reduced mental health is just as important as physical disability. Depression is a common cause of post-operative morbidity (e.g., pain, infections, and impaired QoL) after various conditions.¹⁵ Psychological counselling may be useful to improve expectations, mental health, and QoL for patients with acute DVT, and should be studied in the future. Impaired mental functioning levels after acute DVT are in line with current experiences. Recently, peri-procedural mental support was introduced for patients with acute DVT who are selected for early clot removal in this institution through counselling by a psychologist.

While early clot removal may directly resolve acute complaints, it is also a potential extra stressor due to its invasive character, risk of complications, and possible re-interventions. Evidence of a relationship between timing of questionnaire completion and QoL was missing, suggesting that either the procedure does not affect mental health, or that impaired mental health persists, even after several years. Performance of re-intervention was a significant predictor for lower (worse) SF-36 MCS, emphasising the need to be aware of impaired mental health status in these patients and to prevent re-interventions by patient selection, high percentage of clearance of the vein, proper stent placement, strict follow up, and adequate anticoagulation.

This study has several limitations, including that PROMs were measured at different time points after early clot removal, while, on the other hand, this allowed study of the effect of time since procedure and long term effects. The relatively small sample size of the cohort may have influenced the findings by causing either type I errors (false positives), or type II errors (false negatives). For example, the lack of a significant association between re-intervention and CIVIQ-20 might be a false negative finding. This emphasises the need for future studies with bigger sample sizes. While a response rate of 73.5% was reached in this study, it is also unknown whether QoL was worse or better compared with the 26.5% non-responders. The pretreatment QoL was unknown due to the

unexpected nature of the acute DVT, making it impossible to correct for pre-existing mental and or physical impairments.

CONCLUSION

The PROMs after early clot removal in acute iliofemoral DVT are overall satisfactory; however, impaired physical and mental functioning levels are present in a subgroup. Re-intervention is a predictor for impaired mental functioning. Absence of a relationship between time of questionnaire completion and QoL suggests that impaired functioning levels may persist over time. These findings emphasise the attention mental functioning deserves, besides the widely recognised attention to physical impairment, after invasive treatment for acute iliofemoral DVT, especially when re-interventions take place. Addressing mental health, fatigue, and general health perception directly after the intervention and during follow up may help to improve patients' expectations and quality of life

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SUPPLEMENTARY DATA

Supplementary Table S1. Patient-reported outcomes in all acute deep vein thrombosis patients after endovenous treatment.

SF-36	All patients (n= 39)
Physical Functioning (0-100)	90.0 (IQR: 35.0)
Role-Physical (0-100)	75.0 (IQR: 75.0)
Bodily Pain (0-100)	74.0 (IQR: 49.0)
General Health Perception (0-100)	62.0 (IQR: 35.0)
Vitality (0-100)	60.0 (IQR: 35.0)
Social Functioning (0-100)	87.5 (IQR: 37.5)
Role-Emotional (0-100)	100 (IQR: 66.7)
Mental Health (0-100)	72.0 (IQR: 16.0)
Physical Component Summary (0-100; 50.0 = US reference norm)	50.5 (IQR: 16.6)
Mental Component Summary (0-100; 50.0 = US reference norm)	50.2 (IQR: 14.2)
CIVIQ-20	
Leg Pain (question 1-4)	6.0 (IQR: 7.0)
Physical Activity (question 5-7, 9)	5.0 (IQR: 5.0)
Psychological Activity (question 12-20)	15.0 (IQR: 13.0)
Social Activity (question 8, 10, 11)	4.0 (IQR: 4.0)
Total score (20-100)	29.0 (IQR: 28.0)
Time of questionnaire completion Years	1.8 (IQR: 3.1)

Time of questionnaire completion is shown in years between the primary procedure and completion of the questionnaire. PCS= physical component summary. MCS= mental component summary. Variables presented as median with interquartile range (IQR).

US= United States

Supplementary Table S2. Multivariate regression model for predicting PROMs.

SF-36 PCS (n= 39 patients)	Unstandardized β coefficient $\pm$ standard error	Standardized β coefficient	p-value
Constant	44.2 $\pm$ 13.5		.003
Age Years	-0.3 $\pm$ 0.1	0.04	.85
Sex	3.2 $\pm$ 4.3	0.1	.46
Body Mass Index	-0.08 $\pm$ 0.4	-0.04	.85
Stented	4.6 $\pm$ 6.5	0.1	.49
Re-intervention	-5.4 $\pm$ 5.1	-0.2	.30
Time of questionnaire completion Years	-0.02	-0.1	.52
SF-36 MCS (n= 39 patients)	Unstandardized β coefficient $\pm$ standard error	Standardized β coefficient	p-value
Constant	48.1 $\pm$ 11.4		<.001
Age Years	-0.01 $\pm$ 0.1	-0.03	.90
Sex	-1.1 $\pm$ 3.6	-0.06	.76
Body Mass Index	0.1 $\pm$ 0.3	0.07	.71
Stented	1.9 $\pm$ 5.5	0.07	.74
Re-intervention	-9.5 $\pm$ 4.3	-0.4	.03
Time of questionnaire completion Years	-0.02 $\pm$ 0.02	-0.2	.33
CIVIQ-20 (n= 39 patients)	Unstandardized β coefficient	Standardized β coefficient	p-value
Constant	40.5 $\pm$ 21.2		.07
Age Years	-0.006 $\pm$ 0.2	-0.006	.98
Sex	-0.4 $\pm$ 6.7	-0.01	.96
Body Mass Index	-0.1 $\pm$ 0.6	-0.03	.84
Stented	-9.0 $\pm$ 10.3	-0.2	.39
Re-intervention	16.2 $\pm$ 8.0	0.4	.051
Time of questionnaire completion Years	0.05 $\pm$ 0.04	0.2	.23

Time of questionnaire completion is shown in years between the primary procedure and completion of the questionnaire. PCS= physical component summary. MCS= mental component summary.



4B

Quality of Life after Venous Stenting for Post-thrombotic Syndrome and the Effect of Inflow Disease

(Vascular and Endovascular Surgery, 2023)

Bakas JM, van Montfrans C, Moelker A, van den Bos RR, Malskat WSJ, Verhagen HJM, van Rijn MJE. Quality of Life after Venous Stenting for Post-thrombotic Syndrome and the Effect of Inflow Disease. Vascular and Endovascular Surgery. 2024 Jul;58(5):469-476. Epub 2023 Dec 29. doi: 10.1177/15385744231225802

ABSTRACT

OBJECTIVE

Patients with PTS experience an impaired quality of life (QoL). We aimed to study QoL in patients stented for post thrombotic syndrome (PTS) and analyze the influence of different parameters.

METHODS

Patients stented for PTS after iliofemoral deep vein thrombosis were asked to complete the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and the Short Form Health Survey (SF-36) in this cross-sectional study. All other data were collected retrospectively. Primary endpoints were median CIVIQ-20 and physical (PCS) and mental (MCS) component summary SF-36 scores. The influence of age, sex, and years between the procedure and completion of questionnaire were investigated using a multivariate linear regression model. Wilcoxon signed rank test compared the PCS and MCS with the normative. Effects of inflow from the deep femoral vein (DFV) and/or the femoral vein (FV) on QoL was analyzed in patients with patent stents.

RESULTS

The response rate was 70.3% (n= 45/64). Time period (median) from stenting to questionnaire completion was 6.6 years (IQR: 8.0). Most stents were placed unilateral left-sided (73.3%). For patients with patent stents (n= 42) median CIVIQ-20 was 35.5 (IQR: 17.3), higher than the minimum of 20.0 ($P < .001$). Median PCS of 44.7 (IQR: 14.2) was lower ($P < .001$), and MCS of 55.9 (IQR: 7.1) higher ($P = .001$) than the normative (50.0). Time since stenting and sex were not associated with QoL. Age was a significant predictor [standardized coefficient $\beta = .36$, $P = .04$] for QoL using the CIVIQ-20, but not for the SF-36. Inflow disease did not impact QoL, but patients with occluded stents (n= 3) had poor functioning levels.

CONCLUSION

Quality of life is impaired after venous stenting for PTS, particularly physical functioning, among patients with an open stent, but was similar between patients with good and impaired inflow. Patients with a permanent stent occlusion had the lowest QoL.

INTRODUCTION

Post-thrombotic syndrome (PTS) is the most frequent chronic complication of acute deep vein thrombosis (DVT), occurring in 20 to 50% of iliofemoral DVT patients.¹ Symptoms and signs usually arise within the first year, but may also start decades after the initial DVT.² Preventing DVT and complications, such as PTS, is important based on clinical and economic grounds,³ especially considering the disease's incurability and great impact on relatively young patients.

Patients with PTS experience an impaired quality of life (QoL), which can be similar to other chronic diseases, such as diabetes mellitus, obstructive lung disease, and congestive heart failure.⁴ Treatment mainly focusses on the relief of complaints and prevention of a new DVT by optimized anticoagulation, compression therapy, and lifestyle changes. According to current guidelines of the European Society for Vascular Surgery (ESVS), endovenous treatment should additionally be considered in symptomatic patients with iliofemoral outflow obstruction.⁵

There are various predictors for a poor QoL after DVT, such as development and severity of PTS, iliofemoral DVT, inadequate anticoagulant treatment and incomppliance to compression therapy.⁶ Residual thrombus seems related to impaired QoL⁷ and the risk of PTS development is higher in patients with a more proximal DVT compared to patients with a distal DVT.⁸ Patient-reported outcome measures (PROMs) successfully improved after venous stenting between 3 and 24 months of follow-up in patients with PTS.^{9,10} but the long-term effects are unknown. Whether venous stenting is beneficial for patients with inflow disease, in terms of QoL, is also unknown.

This cross-sectional study evaluates QoL in PTS patients after stenting for iliofemoral outflow obstruction. All other data were collected retrospectively. Years between the procedure and QoL evaluation, as well as inflow from the deep femoral vein (DFV) and/or femoral vein (FV), were studied to evaluate the long-term effect of venous stenting on QoL in patients with patent stents.

METHODS

Cohort

All patients with deep venous stents for PTS in the iliac, iliofemoral and/or caval veins were retrospectively screened from the hospital's first procedure in May 2006 until November 2021. Exclusion criteria were inadequate understanding

of the Dutch language, cognitive impairment, or impossible to invite (e.g. death or living abroad). The remaining patients were asked for informed consent to complete two questionnaires: the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and the Short Form Health Survey (SF-36). Patients with informed consent and completed questionnaires were included in this cross-sectional study. The questionnaires were filled out once at least 3 months after the primary procedure in a cross-sectional design, with varying time-intervals for each patient. Non-responders and patients with incomplete questionnaires were re-contacted once, and excluded if no response was sent back within at least 3 months. This study was approved by the local Medical Ethical board (MEC-2020-0429).

Baseline characteristics were retrospectively collected from medical records: age, sex, body mass index (BMI) during the primary procedure, medical history of diabetes mellitus (DM), medical history of peripheral arterial occlusive disease (PAOD), stent laterality, post-stent anticoagulant therapy, and smoking. All patients underwent recent evaluation of venous stent patency, since it was prospectively recorded as a component of a larger study in which the current study was integrated.¹¹ The STROBE statement for observational studies was used to report the data.¹²

Definitions

Open stents were defined as either primary (open without re-intervention), or secondary patent (open after re-intervention). To assess this, all patients underwent duplex ultrasound (DUS). A small proportion underwent additional contrasted computed tomography venography in case of inconclusive DUS. The term permanent occlusion was used for occluded stents without further options to restore patency. Age was reported in years at time that the questionnaires were completed. Inflow was scored by three authors (JB, AM, and MR) using pre- and/or peri-procedural imaging, including duplex ultrasound, magnetic resonance imaging, computed tomography, phlebography, and/or intravascular ultrasound findings. Inflow disease was defined as impeded flow (presence of post-thrombotic changes) from the DFV and/or FV of the affected limb(s) and discrepancies were resolved after reaching 100% negotiated consensus. Patients with good inflow (absence of post-thrombotic changes) from the DFV and FV of the affected limb(s) were categorized as having no inflow disease.

Stent procedure

Patients with moderate to severe PTS (Villalta ≥ 10), or severe venous claudication, were stented at least 1 year after the initial DVT if iliofemoral and/or caval obstruction was present. All patients received low-molecular-weight heparin

after venous stenting and switched to a vitamin-K-antagonist or direct-oral-anticoagulant after 2 weeks.

Quality of Life

Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) is a validated 20-question disease-specific questionnaire, which assesses lower limb complaints, impact on daily activities, and mental state in chronic venous disease.¹³ It depicts 4 subdomains (leg-pain, physical activity, psychological activity, and social activity) and a total score. The total score ranges between 20 (no complaints) and 100, with higher scores indicating more complaints and a worse QoL.

The SF-36 is a validated 36-question survey for health-related QoL. It yields 8 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and a mental and physical component summary (MCS and PCS).¹⁴ Each domain scores on a scale of 0 to 100, with higher scores indicating a better QoL, as opposed to the CIVIQ-20. The component summaries are normative-based scores. A component summary of 50 is used as a reference norm for the general population of the United States (US).

Statistical Analysis

Data were analyzed using SPSS software version 28.0.1.0 (IBM®). The questionnaire responses and demographics were analyzed using descriptive frequencies. Continuous variables were presented as mean with standard deviation (SD), or median with interquartile range (IQR). Scatterplots and boxplots were used to further visualize patient-reported outcomes. Multivariate regression model was used to test if age, sex, and time between venous stenting and questionnaire completion significantly predicted PROMs, using ANOVA-test to calculate P-values. The SF-36 component summaries were compared with the normative value of 50.0 for the general population of the United States, using a Wilcoxon signed rank test. The SF-36 and CIVIQ-20 outcomes were also compared between patients with and without inflow disease after successful venous stenting (patent stents). The Shapiro-Wilks test was used to test if samples were normally distributed. Non-parametric independent t-test was used to calculate P-values, with statistical significance set at $P < .05$. Missing data were excluded from the analysis.

RESULTS

Cohort

A total of 67 patients underwent venous stenting for PTS, as shown in [Figure 1](#). Three patients were excluded and the remaining 64 patients were invited to complete the CIVIQ-20 and SF-36 questionnaires, which resulted in a response rate of 70.3% ($n = 45/64$). Characteristics of included patients are shown in [Table 1](#). Mean age at time of questionnaire completion was 54 years, most patients were female (80%), and most stents were placed unilateral left-sided (73.3%). None of the patients had medical history of PAOD, and one patient had diabetes mellitus. Time period (median) from venous stenting to questionnaire completion was 6.6 years (IQR: 8.0). Permanent stent occlusion was observed in 3 patients. Data were missing for BMI ($n = 8$ patients) and smoking ($n = 3$ patients).

Figure 1. Flowchart patient inclusion.

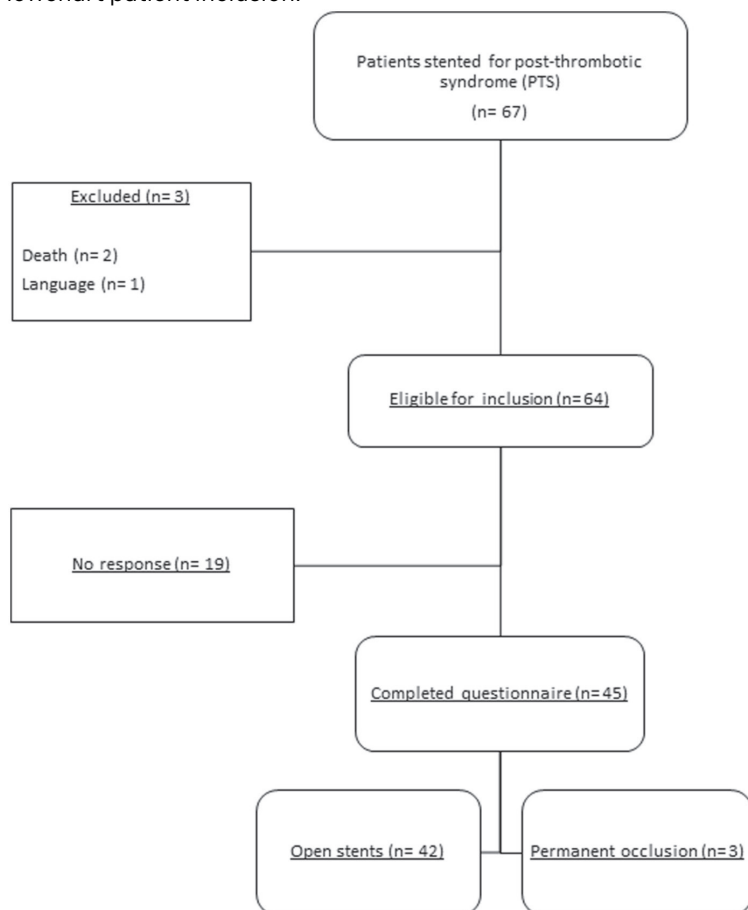


Table 1. Characteristics of Included Patients.

	Post-thrombotic syndrome (n= 45)
Age, years	54 ± (SD 14)
Female	36 (80.0)
BMI *	25.7 (IQR 5.4)
Diabetes	1 (2.2)
PAOD	0 (0)
Smoking *	17 (40.5)
Permanent occlusion	3 (6.7)
Follow-up, years	6.6 (IQR: 8.0)
Stent laterality	
Left (unilateral)	33 (73.3)
Right (unilateral)	3 (6.7)
Bilateral	9 (20.0)
Anticoagulant therapy (post-stent)	
LMWH switched to VKA	41 (91.1)
LMWH switched to DOAC	4 (8.9)

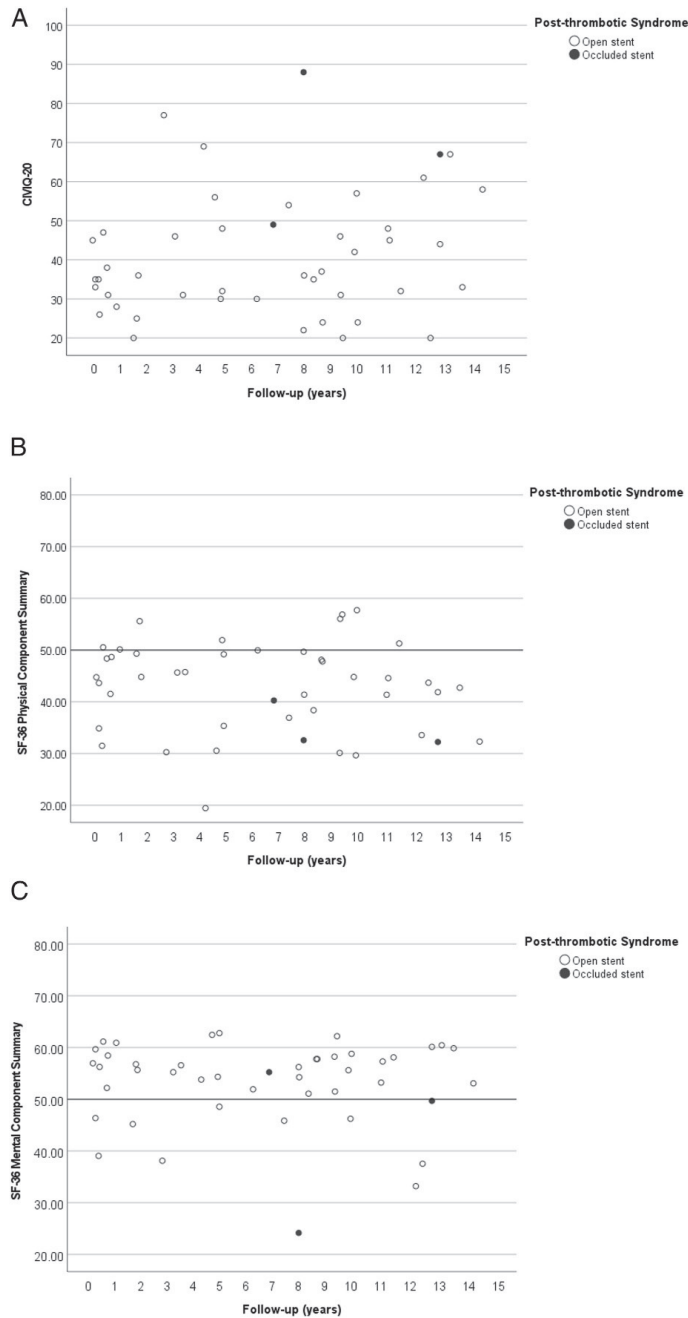
*Categorical variables presented as count (%) and continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR); age and follow-up at time the questionnaire was filled out; PAOD: peripheral arterial occlusive disease; LMWH: low-molecular-weight-heparin; VKA: vitamin-K-antagonist; DOAC: direct-oral anticoagulant; *missing values n= 8 for Body Mass Index (BMI) and n= 3 for smoking.*

Longitudinal Patient-Reported Outcome Measures

Figure 2a. displays a scatterplot for total CIVIQ-20 score (y-axis) vs years between the primary procedure and completion of the questionnaire (x-axis) for patients with open and occluded stents. It shows wide ranges of CIVIQ-20 scores between PTS patients with patent stents. The median CIVIQ-20 of patients with patent stents (n= 42) was 35.5 (IQR: 17.3), significantly higher than the minimum of 20.0 ($P < .001$). The patients with permanent stent occlusion were in the subgroup of patients with the highest CIVIQ-20 scores, indicating more complaints and disabilities of chronic venous disease than patients with open stents (see paragraph 3.3). Sex [standardized coefficient $\beta = .007$, $P = .96$] and years between venous stenting and questionnaire completion [standardized coefficient $\beta = .30$, $P = .08$] did not significantly predict higher CIVIQ-20 (not shown). Age was a significant predictor for CIVIQ-20 [standardized coefficient $\beta = .36$, $P = .04$], indicating higher (thus worse) CIVIQ-20 in older patient.

Figure 2b. shows a scatterplot for SF-36 PCS for each included patient. Median PCS of patients with patent venous stents (n= 42) was 44.7 (IQR: 14.2),

Figure 2. Patient-reported outcome measures in patients with open and occluded venous stents. (A): Total CIVIQ-20 scores plotted against years between the primary procedure and completion of the questionnaire in years. (B): Total SF-36 physical component summary plotted against years between the primary procedure and completion of the questionnaire in years. (C): Total SF-36 mental component summary plotted against years between the primary procedure and completion of the questionnaire in years.



significantly lower than the normative value of 50.0 ($P < .001$). Patients with permanent stent occlusion reported the lowest SF-36 scores, indicating more physical impairments than patients with open stents (see paragraph 3.3). Age [standardized coefficient $\beta = -.28$, $P = .10$], sex [standardized coefficient $\beta = -.22$, $P = .17$], and years between venous stenting and questionnaire completion [standardized coefficient $\beta = -.24$, $P = .15$] did not significantly predict SF-36 PCS (not shown).

Figure 2c. depicts a similar scatterplot for the SF-36 MCS. The median score of MCS was 55.9 (IQR: 7.1) significantly higher than the normative value of 50.0 ($P = .001$). The MCS was scattered for patients with permanent occlusion, with one scoring above, one around, and one below the reference of 50.0. Age [standardized coefficient $\beta = -.03$, $P = .86$], sex [standardized coefficient $\beta = -.12$, $P = .47$], and years between venous stenting and questionnaire completion [standardized coefficient $\beta = -.01$, $P = .96$]. Did not significantly predict SF-36 MCS (not shown).

Inflow Disease

Out of all 42 patients with patent venous stents, 24 had impaired inflow from the DFV and/or FV. The remaining 18 patients had good inflow from both veins. Outcomes of the (subdomains of) SF-36 and CIVIQ-20, between patients with and without inflow disease, are compared in Table 2. For patients without inflow disease, the median PCS was 44.1 (IQR: 9.5), median MCS 56.1 (IQR: 8.8), and total CIVIQ-20 was 34.0 (IQR: 22.0), after a median time of 8.8 years after venous stenting (IQR: 9.5). No significant differences were found compared to patients with inflow disease (median PCS of 43.8 (IQR: 16.8), median MCS of 55.9 (IQR: 7.1), and total CIVIQ-20 was 36.0 (IQR: 22.3)), after a median time of 5.4 years after venous stenting (IQR: 7.6). Also no differences were found between any of the SF-36 subdomains.

Table 2. Patient reported outcomes for patients with patent venous stents: with and without inflow disease of the (deep) femoral vein.

SF-36	Good inflow DFV/FV (n= 18)	Inflow disease DFV/ FV (n= 24)	p-value
Physical Functioning (0-100)	77.5 (IQR: 36.3)	75.0 (IQR: 45.0)	.15
Role-Physical (0-100)	100 (IQR: 56.3)	100 (IQR: 50.0)	.77
Bodily Pain (0-100)	62.0 (IQR: 14.8)	72.0 (IQR: 30.3)	.58
General Health (0-100)	58.5 (IQR: 29.5)	59.5 (IQR: 33.3)	.92
Vitality (0-100)	55.0 (IQR: 17.5)	67.5 (IQR: 33.3)	.31
Social Functioning (0-100)	81.3 (IQR: 38.1)	87.5 (IQR: 46.9)	.49
Role-Emotional (0-100)	100 (IQR: 8.3)	100 (IQR: 25.0)	.84
Mental Health (0-100)	82.0 (IQR: 17.0)	84.0 (IQR: 12.0)	.76
Physical Component Summary (0-100; 50.0 = US reference norm)	44.1 (IQR: 9.5)	43.8 (IQR: 16.8)	.88
Mental Component Summary (0-100; 50.0 = US reference norm)	56.1 (IQR: 8.8)	55.9 (IQR: 7.1)	.99
CIVIQ-20			
Leg Pain (Q1-4)	8.0 (IQR: 5.5)	8.0 (IQR: 4.8)	.53
Physical Activity (Q5-7, 9)	8.0 (IQR: 5.5)	7.0 (IQR: 6.0)	.91
Psychological Activity (Q12-20)	15.5 (IQR: 7.5)	16.0 (IQR: 8.5)	.21
Social Activity (Q8, 10, 11)	5.0 (IQR: 5.3)	5.5 (IQR: 5.0)	.26
Total score (20-100)	34.0 (IQR: 22.0)	36.0 (IQR: 22.3)	.45
Follow-up * Years	8.8 (IQR: 9.5)	5.4 (IQR: 7.6)	.66

Variables presented as median with interquartile range (IQR). DFV= deep femoral vein. FV= femoral vein. Q= question. US= United States. * between stenting procedure and questionnaire completion.

Permanent Stent Occlusion

Table 3. shows patients with a permanent stent occlusion (n= 3). Two were female (32 and 63 years old) and one male (49 years old). Time between the primary stent procedure and completion of the questionnaire were 6.7, 12.7, and 7.8 years. The reported CIVIQ-20 scores were 49, 67, and 88, which are all three above the median CIVIQ-20 for patients with patent venous stents (35.5, IQR: 17.3). The physical component summaries (40.3, 32.2, and 32.6) were below the reference normative of 50, and also below the median of patients with patent venous stents (44.7, IQR: 14.2). The median MCS was 24.2 for one patient with multiple comorbidities and similar or above the reference norm of 50.0 for the other two patients (scores of 55.2 and 49.7). All three MCS of patients with permanent stent occlusion were below the median score of patients with patent venous stents 55.9 (IQR: 7.1). Permanent stent occlusion was likely related to pre-existent poor inflow for two and inability to restart anticoagulant therapy for one patient.

Table 3. Characteristics and outcomes of patients with a permanent stent occlusion.

Patient	Remarks	Patient reported outcome measures
Female patient 32 years old PTS, left limb	Stent • Wallstent • Placed across the inguinal ligament • Good inflow DFV and FV. Hematological • Heterozygous MTHFR mutation • Anticoagulants: VKA Comorbidity: multiple VTE, complicated pregnancy, miscarriage. Cause: cessation of anticoagulant therapy because of blood loss during pregnancy	CIVIQ-20 total score: 49 SF-36 mental component summary: 55.2 physical component summary: 40.3 Follow-up 6.7 years
Female patient 63 years old PTS, bilateral	Stent • Wallstent, Smart and SinusXL stents. • Both sides placed above the inguinal ligament • Impaired inflow of left DFV and FV. • Good inflow of the right DFV and FV. Hematological • Antiphospholipid syndrome • Anticoagulants: VKA Comorbidity: multiple VTE, alopecia androgenica, hirsutism, monoclonal gammopathy. Cause: pre-existent poor stent inflow	CIVIQ-20 total score: 67 SF-36 mental component summary: 49.7 physical component summary: 32.2 Follow-up 12.7 years
Male patient 49 years old PTS, left limb	Stent • Wallstent • Placed across the inguinal ligament • Poor inflow of the DFV, impaired inflow of the FV Hematological • Thrombophilia not tested. • Anticoagulants: dual antiplatelet and VKA. Comorbidity: former addiction to intravenous drugs, myocardial infarct, endocarditis, osteomyelitis, thoracic empyema, femoral fractures treated by surgical reposition and fixation. Cause: pre-existent poor stent inflow	CIVIQ-20 total score: 88 SF-36 mental component summary: 24.2 physical component summary: 32.6 Follow-up 7.8 years

Age and follow-up at time the questionnaire was filled out. PTS: post-thrombotic syndrome. VTE: venous thromboembolism. VKA: vitamin-K-antagonist; DFV= deep femoral vein; FV: femoral vein.

DISCUSSION

Impaired QoL was found in PTS patients particularly in terms of physical functioning, regardless of long-term stent patency. Mental disabilities were less common after venous stenting and QoL was not influenced by the time interval between the procedure and questionnaire completion. Patients with inflow disease, but open stents, had a similar QoL as patients with a good inflow. Patients with a permanently occluded stent had the poorest QoL.

Median PCS was below the reference value of 50 in the first three quartiles (75.0%) of our cohort. Improved scores were previously reported on several SF-36 domains after venous stenting for PTS, such as physical functioning, role-physical, and bodily pain.¹⁵ These results kept improving after two years of follow-up after venous stenting.¹⁰ In our study, we did not find a relationship between the time of questionnaire completion and SF-36 component summaries. This suggests that patients reach a stable phase with consistent functioning levels, where the timing of assessment after stent placement no longer impacts QoL. However, this observation should be considered an assumption, because the different time intervals were not assessed in the same patients, but across patients.

Improved outcomes after stenting were also reported in two studies using the CIVIQ-20 questionnaire, although the follow-up was limited to 3 and 12 months.^{16,17} Patients with patent stents from the present study had comparable CIVIQ-20 to those reported in previous studies after venous stenting. The time of questionnaire completion again not significantly related to QoL when using the CIVIQ-20 questionnaire in our cohort.

The physical impairments in a considerable group of PTS patients did not seem to be attributable to inflow disease. There were no significant differences in PROMs between patients with good and impaired inflow, in case of patent stents. This may be explained by the higher risk of PTS development in patients with a more proximal DVT compared to patients with a distal DVT.⁸ From a hemodynamical perspective, the relief of iliofemoral outflow obstruction in patients with inflow disease, is likely to change them into 'distal DVT' patients if their stents remain open, also in terms of QoL.

While future studies are needed to identify patients who will benefit the most from venous stents (e.g. by predicting QoL), this study reveals that physical disabilities are common in endovascular treated PTS patients, at different time points after the procedure, even if stents are patent. These results emphasize the importance of continuously monitoring QoL during follow-up after venous stenting. Adjunctive treatment, such as compression therapy and lifestyle changes, should be specifically encouraged in patients with lowered QoL due to physical disabilities. Patients with PTS who were compliant to compression stockings had similar QoL scores to patients without PTS in a previous study.¹⁸ Additionally, physical activity might be promoted by the use of smart watches and similar devices, which are useful for both monitoring and supporting healthy lifestyle interventions.¹⁹

The poorest QoL was found in patients with a permanent stent occlusion. Previously, reasons for re-thrombosis were classified and scored as related to technical issues, poor inflow, coagulation disorders, and/or inadequate anticoagulant therapy. Reasons why re-opening was not possible in these three patients were poor inflow for two and inability to restart anticoagulant therapy for one patient. Our findings emphasize the importance of preserving stent patency specifically by paying attention to inflow and optimal anticoagulant treatment. In cases where the loss of patency is likely, invasive treatment should be avoided.

This study has several limitations. The cross-sectional study design prevented us from comparing QoL before and after venous stenting. The included cohort spans over 15 years of time, presumably leading to heterogeneity in patient selection, treatment technique, and follow-up. The long time interval between the procedure and questionnaire completion is at the same time the unique part of the study. The small size of the groups limited the ability to adjust for potential confounders, although the poorest QoL was found after permanent occlusion, suggesting to support an association between venous patency and PTS severity.²⁰ While inflow was measured before and during the procedure, allocation to presence or absence of inflow disease was performed retrospectively for the purpose of this study. It is unknown if QoL differs between patients who denied study participation and those who consented, but the response rate suggests a low likelihood of non-response bias, which seems good compared to other studies.^{21,22}

CONCLUSION

Impaired physical functioning is common after endovenous stenting for PTS, independent from time since procedure. Continuous monitoring and consultation during follow-up are necessary to consider adjunctive treatment, regardless of stent patency and inflow disease. Identifying predictors for improved QoL after endovenous interventions are needed to determine suitable candidates for these procedures. Patients with inflow disease may still benefit from venous stenting in terms of QoL, but selection is key as inflow is related to re-interventions for in-stent thrombosis.¹¹ Preventing stent occlusion is crucial since patients with occluded stents had poor QoL. To achieve this, it should be recommended to avoid venous stenting in high-risk patients prone to stent failure. Identifying these high-risk patients should be the subject of future studies.

4B

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PART IV

INFLOW DISEASE IN POST-THROMBOTIC SYNDROME



Venous Stents Placed for Post-thrombotic Syndrome: The Role of Inflow Disease on Patency

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ABSTRACT

PURPOSE

To identify the risk of deep femoral vein (DFV) and/or femoral vein (FV) inflow disease on venous stent patency loss in postthrombotic syndrome (PTS).

MATERIALS AND METHODS

This single-center retrospective study included limbs with iliofemoral and ilio caval stents for PTS. Single-vessel and double-vessel inflow disease were defined on the basis of imaging of possible postthrombotic changes in the DFV/FV. Endpoints were 1-year primary patency (open stents without reintervention) and secondary patency (open stents with or without reintervention). Event-free survival was estimated using Kaplan-Meier methods (log-rank test). Univariate and multivariate binary logistic regression were conducted to estimate the effects of various covariates on the risk of primary patency loss.

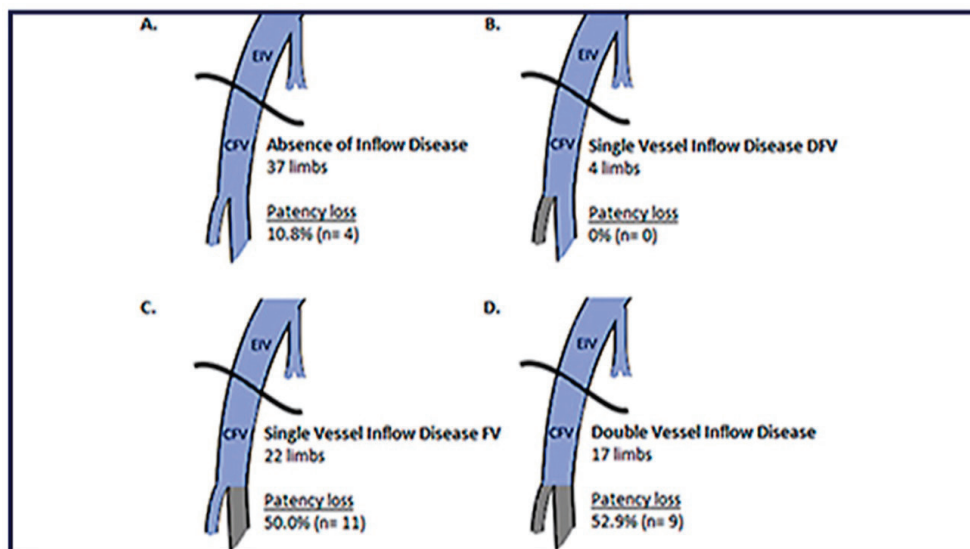
RESULTS

Eighty limbs were included: 37 limbs (46%) without inflow disease, 26 limbs (33%) with single-vessel inflow disease, and 17 limbs (21%) with double-vessel inflow disease. One-year primary patency was higher for limbs without inflow disease (89.2%) than for limbs with single-vessel inflow disease (57.7%; $P = .002$) and double-vessel inflow disease (47.1%; $P < .001$). No significant differences were found for secondary patency. Inflow disease predicted 1-year primary patency loss (odds ratio [OR], 7.17; 95% CI, 2.16–23.78; $P = .001$; univariate). Inflow disease of the FV was the only significant predictor after multivariate analysis (OR, 10.99; 95% CI, 2.59–46.74; $P = .001$).

CONCLUSIONS

Inflow disease increases the risk of patency loss within the first year after treatment with venous stents for PTS. Inflow should be discussed with patients to improve decision making and expectations.

GRAPHICAL ABSTRACT



RESEARCH HIGHLIGHTS

- Inflow disease was evaluated in a total of 80 limbs (68 patients) after venous stent placement for postthrombotic syndrome.
- Primary patency within the first year was significantly higher for patients without inflow disease (89.2%) than for those with single-vessel (57.7%, $P = .002$) and double-vessel (47.1; $P < .001$) inflow disease; however, secondary patency was similar.
- Preoperative sufficient inflow of the deep femoral vein and femoral vein is important in postthrombotic syndrome because inflow disease increases the risk for loss of primary stent patency.

STUDY DETAILS

Study type: Retrospective, observational, cohort study

Level of evidence (Oxford v2.1): 3 (SIR-C)

INTRODUCTION

Postthrombotic syndrome (PTS) is a serious complication following acute deep vein thrombosis (DVT) that causes various symptoms and signs, such as pain, edema, and/or venous ulceration of the lower limb.¹ Stent placement should be considered for patients with iliofemoral venous outflow obstruction and severe PTS.² Primary patency rate—an open stent without reintervention—ranges from 59% to 94% after these procedures.³

Reinterventions are mostly performed within the first year⁴ and can possibly be prevented.^{4,5} Missed postthrombotic lesions (e.g. lesions that should have been covered with a stent) and poor inflow from the deep femoral vein (DFV) and/or femoral vein (FV) (e.g. lesions that remain caudal to an optimal stent placement, also referred to as inflow disease) are potential causes of stent occlusion.⁶⁻⁸ In addition to anticoagulation compliance, physicians should aim for adequate treatment of venous lesions (no missed postthrombotic lesions) and proper patient selection (sufficient inflow) to prevent loss of patency.

Objective criteria for determining adequate inflow are currently missing, with a lack of consistency in the methods used for inflow assessment across previous studies.^{6,8-10} Evaluation of inflow possibly remains challenging due to high variability in anatomy, severity, and extension of postthrombotic lesions.^{11,12} Details of the scoring methods used across previous studies were not reported, or grading was conducted without distinguishing between inflow of the DFV and FV.^{6,9} One study⁸ classified inflow as single-vessel (DFV or FV) or double-vessel (DFV and FV).

In this study, inflow disease of the DFV and FV was scored, aiming to assess the risk of inflow disease on stent patency loss. Secondly, single- and double-vessel inflow disease were studied as predictors of loss of patency.

MATERIALS AND METHODS

Cohort

This retrospective single-center cohort study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹³ Patients treated with venous stents for obstructive iliac, iliofemoral, and/or iliocaaval PTS between May 2006 (first procedure) and November 2022 were eligible for inclusion if sufficient imaging was available to appropriately score inflow disease of the DFV and FV. Inflow of the DFV and

FV was scored using phlebography, computed tomography (CT) venography, magnetic resonance (MR) venography, and/or duplex ultrasound (US). In the earlier years of this cohort, a combination of MR venography and phlebography was used to assess inflow, although selective catheterization of the DFV was not consistently performed. In later years, duplex US protocol was standardized to visualize both the DFV and FV, and MR venography improved, limiting venography (with selective catheterization of the DFV) to cases where DFV inflow was inconclusive. Exclusion criteria were duplex US/CT venography follow-up at less than 1 year and venous stents placed for indications other than PTS (e.g., acute DVT, nonthrombotic iliac vein lesions, or external venous compression by malignancies).

Data on patient and procedural characteristics (including age, sex, body mass index [BMI], thrombophilia, malignance, smoking history, stent localization, and type and length of venous stents) were retrospectively collected from medical records. Venous stents were only considered for patients with moderate or severe PTS (Villalta scale score, ≥ 10)¹ or severe venous claudication (disabling maximum walking distance) at least 1 year after the DVT. All potential candidates for venous stent treatment were evaluated in a multidisciplinary meeting, where inflow was assessed using duplex US, CT venography, MR venography, and/or phlebography. Only limbs with minimal trabeculation of the common FV were treated because endophlebectomy was not performed at the treating center.

Two previous studies^{4,14} reported quality of life in 66.2% of the current cohort ($n = 45$ patients) and long-term stent patency in 85% of the cohort ($n = 68$ limbs), focusing on limbs treated until November 2021. The current study includes an in-depth analysis on inflow disease in patients with PTS. The local Medical Ethics Committee approved the study.

Treatment and follow-up

Since 2017, intravascular US has been used in all procedures. Heparin was administered intravenously during stent placement. Incidentally, in cases of double-vessel inflow disease and minimal trabeculation below the femoral confluence into one of the vessels, with otherwise a normal caliber without postthrombotic changes, the stent was placed into that vessel (mainly affecting the DFV). After the procedure, patients were initiated on low-molecular-weight heparin (LMWH) therapy immediately and switched to oral anticoagulant therapy (vitamin K antagonist or direct oral anticoagulant) after 2 weeks in case of patent stents. Stent patency was primarily assessed with duplex US using gray scale, color Doppler, and pulse wave velocity. Loss of phasic flow at the level

of the common FV warranted an in-depth investigation of the stent, as well as reoccurrence of symptoms. If the stent could not be completely visualized with duplex US, additional imaging (CT venography/venography) was performed. Also for asymptomatic patients or those without loss of phasic flow where the stent was not visualized (e.g. obesity or bowel gas), a low threshold was set to obtain additional imaging. Anticoagulant therapy was continued for at least 1 year. For some patients, antiplatelet therapy was added after earlier procedures, but currently antiplatelet therapy is not part of standard postprocedural antithrombotic management.

Dedicated venous stents

All procedures with the exclusive use of self-expandable nitinol stents developed for the venous system were considered as treatment with “dedicated venous stents.” The following dedicated venous stents were used for the patient cohort: Abre (Medtronic, Minneapolis, Minnesota), Beyond (Bentley InnoMed, Hechingen, Germany), Blueflow (plus medica, Düsseldorf, Germany), Veniti Vici (Boston Scientific, Marlborough, Massachusetts), Venovo (BD, Franklin Lakes, New Jersey), and Sinus-XL (optimed, Ettlingen, Germany). From 2017 onward, dedicated venous stents were consistently used. In earlier years, nondedicated venous stents including the Wallstent (Boston Scientific) and arterial/venous stents (Viabahn [Gore Medical, Flagstaff, Arizona], Fluency [BD], Protégé [Medtronic], and S.M.A.R.T. [Cordis, Miami Lakes, Florida]), had been used.

Primary patency loss

Primary patency was defined as the percentage of limbs with open stents without a reintervention. Reinterventions were performed for obstruction (>50%) or stent occlusion. Reintervention was also considered for asymptomatic patients with an obstruction (>50%). Flow lumen downsized to the inflow vessel was not considered significant and was not treated. A stenosis >50% without inflow disease was treated, also for asymptomatic patients. Reinterventions included thrombolysis and/or percutaneous transluminal venoplasty, with or without additional stent implantation. Secondary patency was defined as the percentage of limbs with open stents with or without reintervention, whereas permanent occlusion was defined as the percentage of limbs with stent occlusion without further options to restore patency.

Definitions: procedure characteristics

Presence or absence of inflow disease was retrospectively scored by 3 contributors (J.M.B., A.M. (acknowledgements), M.J.E.v.R.) using available preprocedural and periprocedural imaging (phlebography, CT venography, MR venography, and/or duplex US). Postinterventional imaging was not used to assess

inflow disease in this study. The vein was classified as “good” if postthrombotic changes were absent in a normal caliber vessel, as “poor” if postthrombotic obstructions were present in a small caliber vein, and as “fair” when the vein did not fit into either category (e.g. postthrombotic changes with a normal caliber vessel).⁹ If a stent landed into an inflow vessel, covering all trabeculation at the confluence, and the remaining vein had a normal caliber, the vein was scored as “good.” Disagreements were resolved by negotiation to consensus to improve reliability in the absence of objective criteria. “Absence”/“no inflow disease” indicated that both DFV and FV were classified as “good.” “Single-vessel inflow disease” meant that 1 of the inflow vessels (DFV or FV) was classified as poor or fair, whereas the other was rated as good. For “double-vessel inflow disease,” both DFV and FV were classified as fair or poor.

Outcomes

The primary endpoints were primary and secondary patency within 1 year after venous stent implantation. Outcomes for single-vessel and double-vessel inflow disease were compared with limbs without inflow disease. Secondary outcomes were risk factors for primary patency loss.

Statistical analysis

Categorical variables were presented as count with percentage and compared using Pearson chi-square or Fisher exact test. Continuous variables were presented as mean with SD or median with interquartile range. The Shapiro-Wilk test was used to test the sampling distribution, with the Student t-test used for normally distributed and the Mann-Whitney U test used for skewed data. CIs of 95% were used and statistically significant if $P < .05$. Primary and secondary patency were estimated by Kaplan-Meier methods and compared with the log-rank (Mantel-Cox) test.

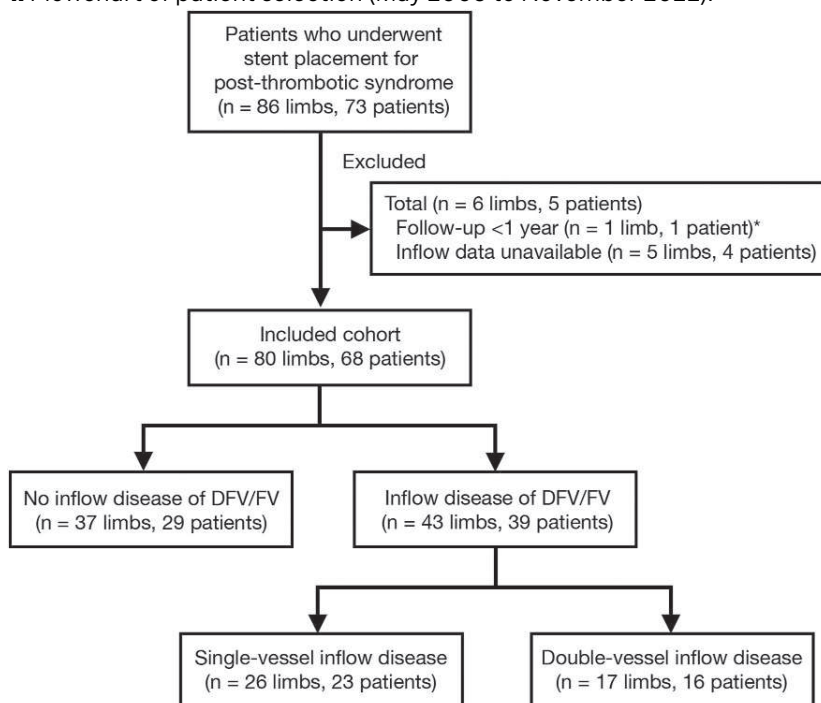
Univariate and multivariate binary logistic regression were performed to estimate the effects of various covariates (age, sex, stent laterality, stent localization across the inguinal ligament, length of stents [mm], use of arterial stents, and presence of inflow disease of the DFV/FV) on the risk for loss of primary patency. Missing variables were excluded from the analysis (SPSS software, version 28.0.1.0, IBM, Armonk, New York).

RESULTS

Cohort

A total of 80 limbs (68 patients) were included, as shown in [Figure 1](#). Good inflow of both DFV and FV was present in 37 limbs (46%). Inflow disease of the DFV and/or FV was present in 43 limbs (54%): 26 limbs (33%) had single-vessel inflow disease, and 17 limbs (21%) had double-vessel inflow disease. Dedicated venous stents were used for 44 limbs (55.0%), and nondedicated venous stents were used for 36 limbs (45.0%). The following stents were used during treatment with nondedicated venous stents: for 17 limbs, only Wallstents were used; for 11 limbs, Wallstents were combined with a dedicated venous stent. Arterial stents were used for 8 limbs, occasionally combined with a Wallstent or dedicated venous stent: S.M.A.R.T. stents exclusively ($n = 2$), Viabahn combined with Fluency ($n = 2$), S.M.A.R.T. combined with Sinus-XL ($n = 1$), S.M.A.R.T. combined with Wallstent and Sinus-XL ($n = 1$), and Protégé combined with Sinus-XL ($n = 2$). Arterial stents were deployed in 6 limbs without inflow disease and 2 limbs with double-vessel inflow disease.

Figure 1. Flowchart of patient selection (May 2006 to November 2022).



* one patient died within 1 year. DFV= deep femoral vein. FV= femoral vein.

Missing data affected length of stents ($n = 7$ limbs), smoking ($n = 3$ limbs), and BMI ($n = 9$ limbs).

Absence versus single-vessel and double-vessel inflow diseases

Characteristics of limbs with single-vessel and double-vessel inflow disease of the DFV/FV were compared with limbs without inflow disease in [Table 1](#). Clinical examples are illustrated for absence of inflow disease ([Figure 2a, b](#)), single-vessel inflow disease ([Figure 2c](#)), and double-vessel inflow disease ([Figure 3a–c](#)). Limbs with single-vessel inflow disease were significantly more frequently treated with stents across the inguinal ligament compared with limbs without inflow disease ($n = 17$ [45.9%] vs $n = 20$ [76.9%]; $P = .02$). No significant differences were found for age, sex, BMI, thrombophilia, malignancy, smoking, dedicated venous stents, laterality, length of stents, and postprocedural anticoagulant therapy compared with patients or limbs without inflow disease. For double-vessel inflow disease, no significant differences were found in patient and limb characteristics compared with limbs without inflow disease. Primary patency loss within 1 year was 10.8% ($n = 4$) for limbs without inflow disease ($n = 37$), 0% ($n = 0$) for limbs with single-vessel inflow disease of the DFV ($n = 4$), 50.0% ($n = 11$) for limbs with single-vessel inflow disease of the FV ($n = 22$), and 52.9% ($n = 9$) for limbs with double-vessel inflow disease ($n = 17$), as visualized in [Figure 4a–d](#). Postprocedural anticoagulants used were LMWH switched to a vitamin K antagonist for 36 limbs (97.3%) without inflow disease, 26 limbs (100%) with single-vessel inflow disease, and 16 limbs (94.1%) with double-vessel inflow disease. For 1 limb (2.7%) without inflow disease and 1 limb with double-vessel inflow disease (5.9%), LMWH was switched to a direct oral anticoagulant. Postprocedural antiplatelet therapy was used in 11 limbs (29.7%) without inflow disease, 7 limbs (26.9%) with single-vessel inflow disease, and 7 limbs (41.2%) with double-vessel inflow disease.

Table 1. Absence, single-vessel inflow disease, or double-vessel inflow disease.

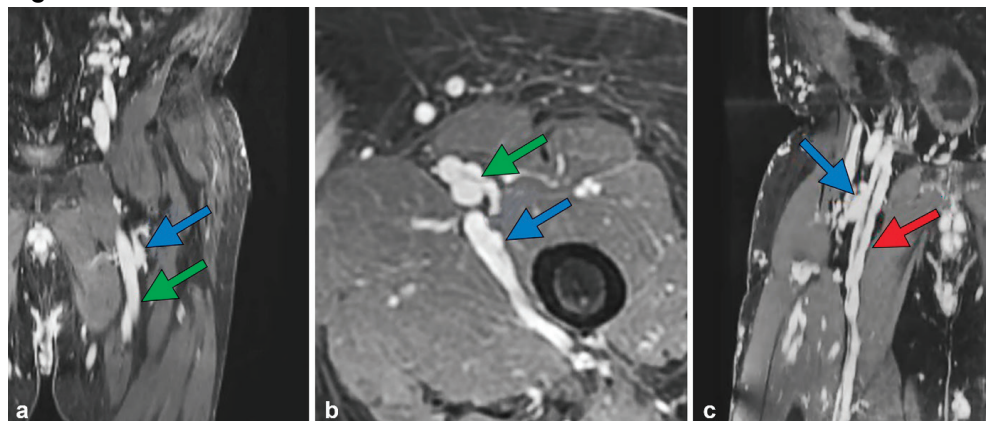
Patient	Inflow disease DFV and/or FV				
	Absence (reference) n= 37	Single vessel (DFV/FV) n= 26 DFV, n= 4 FV, n= 22	P value	Double vessel (DFV and FV) n= 17	P value
Age	47 ± 15.4	43 ± 15.1	.29	46 ± 14.7	.83
Female sex	26 (70.3)	18 (69.2)	.99	15 (88.2)	.19
Body mass index	27 ± 4.6	28 ± 5.3	.74	30 ± 5.3	.09
Thrombophilia	12 (50.0) n= 13 not tested	7 (31.8) n= 4 not tested	.25	9 (69.2) n= 4 not tested	.32
Malignancy	4 (10.8)	1(3.8)	.39	0 (0)	.30
Smoking current/ former*	12 (34.3)	11 (44.0)	.59	8 (47.1)	.54
Left-sided	26 (70.3)	18 (69.2)	.99	16 (94.1)	.08
Stent across IL	17 (45.9)	20 (76.9)	.02	11 (64.7)	.25
Venous stents, dedicated	23 (62.2) n= 6 [†]	15 (57.7)	.80	6 (35.3) n= 2 [†]	.08
Length of stents (mm)*	222 ± 109	225 ± 102	.99	245 ± 95	.23

Note - Fisher Exact test was used for categorical variables. Student t-test was used for continuous variables. Malignancy included either oncological medical history or current diagnosis. Smoking included either current or former smokers. DFV= deep femoral vein; FV= femoral vein; IL= inguinal ligament.

* missing values excluded : n= 3 for smoking; n= 7 for length of stents; n= 9 for body-mass index.

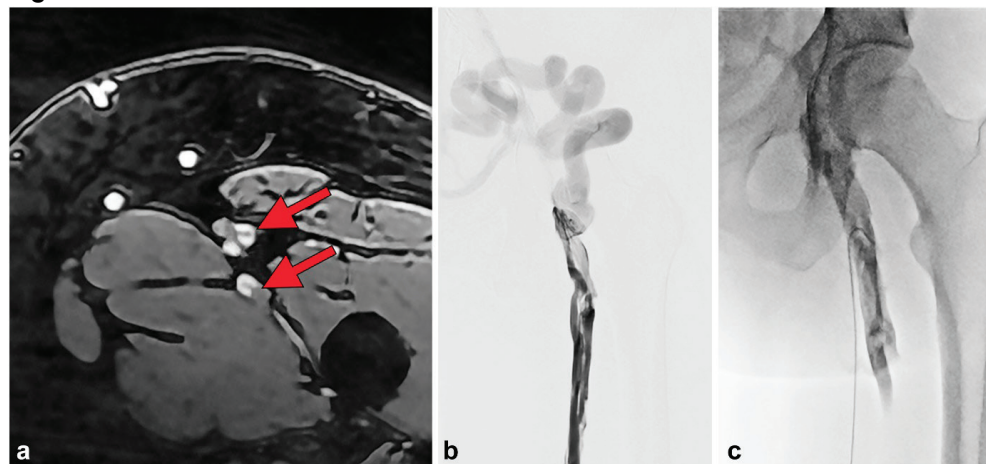
[†] Nondedicated stents were arterial stents for 6 limbs with absence of inflow disease, 2 limbs with double-vessel inflow disease.

Figure 2: Absence of inflow disease:



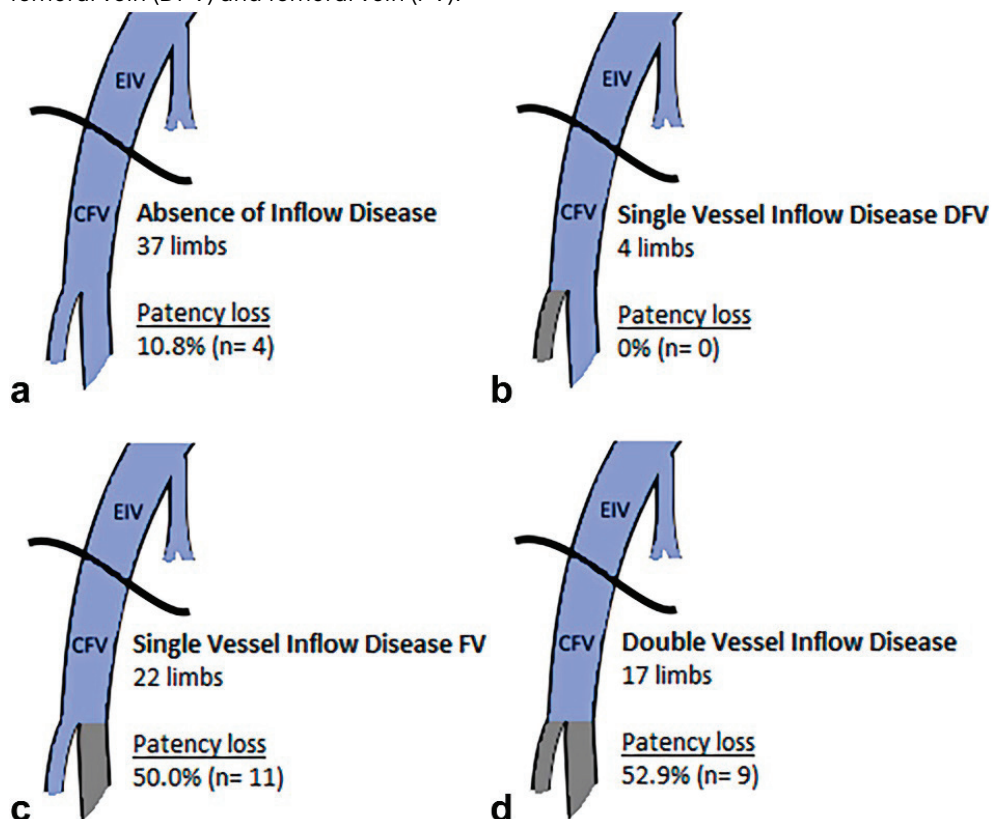
(a) coronal and **(b)** axial venous contrast-enhanced T1 magnetic resonance (MR) imaging, with blue arrow indicating an open deep femoral vein and green arrow indicating an open femoral vein. **(c)** single-vessel inflow disease: coronal venous contrast-enhanced T1 MR imaging, with blue arrow indicating a normal size deep femoral vein without trabeculation and red arrow indicating full-length trabeculation of the femoral vein.

Figure 3: Double-vessel inflow disease:



(a) axial venous contrast-enhanced T1 magnetic resonance (MR) imaging, with red arrows indicating trabeculation in both the deep femoral vein and femoral vein (FV). **(b)** trabeculation of the FV confirmed with contrast phlebography. **(c)** contrast phlebography demonstrating trabeculation of the deep FV confirmed after selective catheterization.

Figure 4: Loss of primary patency within 1 year per type of inflow disease of the deep femoral vein (DFV) and femoral vein (FV):



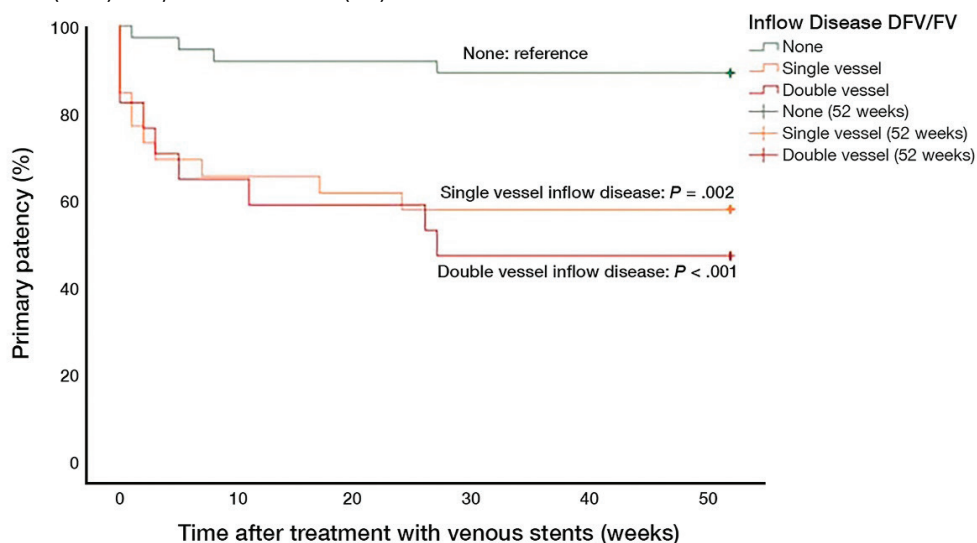
(a) absence of inflow disease, **(b)** single-vessel DFV inflow disease, **(c)** single-vessel FV inflow disease, **(d)** double-vessel inflow disease.

CFV = common femoral vein; EIV = external iliac vein.

Patency within 1 year after treatment with venous stents

Limbs with single-vessel inflow disease had a significantly poorer primary stent patency within the first year (57.7%) compared with limbs without inflow disease (89.2%; $P = .002$), as shown in Figure 5. One-year primary patency was also lower in limbs with double-vessel inflow disease (47.1%) than in those without inflow disease (89.2%; $P < .001$). Loss of primary patency occurred within the first 30 weeks following treatment with venous stents in all cases.

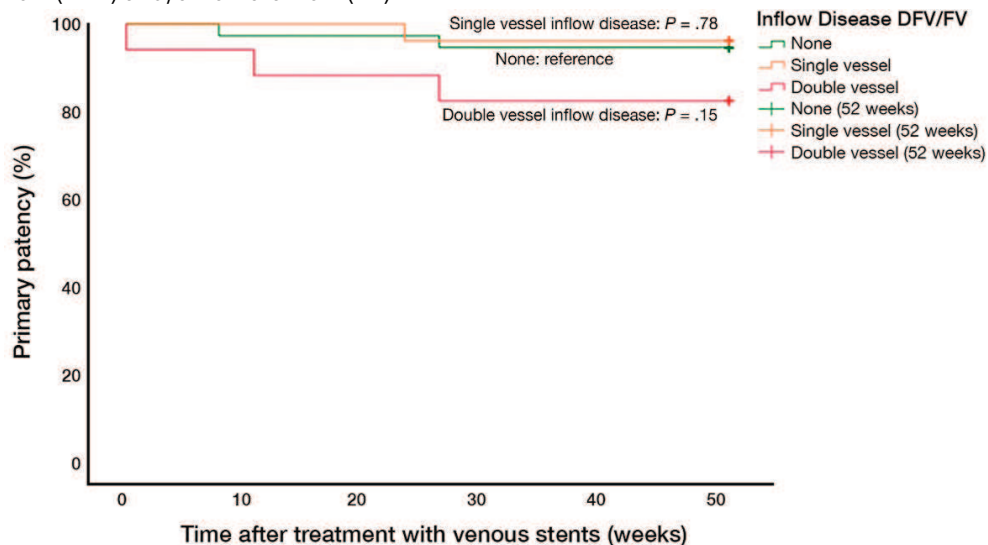
Figure 5: Primary patency within the first year after treatment with venous stents: absence, single-vessel inflow disease, or double-vessel inflow disease of the deep femoral vein (DFV) and/or femoral vein (FV).



	Baseline	10 weeks	20 weeks	30 weeks	40 weeks	50 weeks	52 weeks
● No inflow disease	37 (0)	34 (0)	34 (0)	33 (0)	33 (0)	33 (0)	33 (0)
Re-intervention/occlusion	0	3	3	4	4	4	4
Cum. prop. surviving	-	0.92 ± 0.05	0.92 ± 0.05	0.89 ± 0.05	0.89 ± 0.05	0.89 ± 0.05	0.89 ± 0.05
± standard error							
● Single vessel inflow disease	26 (0)	17 (0)	16 (0)	15 (0)	15 (0)	15 (0)	15 (0)
Re-intervention/occlusion	0	9	10	11	11	11	11
Cum. prop. surviving	-	0.65 ± 0.09	0.62 ± 0.10	0.58 ± 0.10	0.58 ± 0.10	0.58 ± 0.10	0.58 ± 0.10
± standard error							
● Double vessel inflow disease	17 (0)	11 (0)	10 (0)	8 (0)	8 (0)	8 (0)	8 (0)
Re-intervention/occlusion	0	6	7	9	9	9	9
Cum. prop. surviving	-	0.65 ± 0.12	0.59 ± 0.12	0.47 ± 0.12	0.47 ± 0.12	0.47 ± 0.12	0.47 ± 0.12
± standard error							

For secondary patency within the first year, no significant differences were found between limbs without inflow disease (94.6%), compared with those with single-vessel inflow disease (96.2%) and those with double-vessel inflow disease (82.4%), as shown in [Figure 6](#). Multiple reinterventions were performed for 15 limbs: 2 reinterventions were required for 13 limbs and 3 reinterventions were required for 2 limbs. Multiple reinterventions were performed for 10.8% ($n = 4$) of the limbs without inflow disease, 19.2% ($n = 5$) of the limbs with single-vessel inflow disease, and 35.3% ($n = 6$) of the limbs with double-vessel inflow disease.

Figure 6: Secondary patency within the first year after treatment with venous stents: absence, single-vessel inflow disease, or double-vessel inflow disease of the deep femoral vein (DFV) and/or femoral vein (FV).



	Baseline	10 weeks	20 weeks	30 weeks	40 weeks	50 weeks	52 weeks
● No inflow disease	37 (0)	36 (0)	35 (0)	35 (0)	35 (0)	35 (0)	35 (0)
Permanent occlusion	0	1	2	2	2	2	2
Cum. prop. surviving ± standard error	-	0.97 ± 0.03	0.95 ± 0.04	0.95 ± 0.04	0.95 ± 0.04	0.95 ± 0.04	0.95 ± 0.04
● Single vessel inflow disease	26 (0)	26 (0)	26 (0)	25 (0)	25 (0)	25 (0)	25 (0)
Permanent occlusion	0	0	0	1	1	1	1
Cum. prop. surviving ± standard error	-	-	-	0.96 ± 0.04	0.96 ± 0.04	0.96 ± 0.04	0.96 ± 0.04
● Double vessel inflow disease	17 (0)	16 (0)	15 (0)	14 (0)	14 (0)	14 (0)	14 (0)
Permanent occlusion	0	1	2	3	3	3	3
Cum. prop. surviving ± standard error	-	0.94 ± 0.06	0.88 ± 0.08	0.82 ± 0.09	0.82 ± 0.09	0.82 ± 0.09	0.82 ± 0.09

Predictors for 1-year primary patency loss

Inflow disease was a significant predictor in an univariate binary logistic regression for loss of primary patency within 1 year after venous stent implantation (odds ratio [OR], 7.17; 95% CI, 2.16–23.78; $P = .001$; Table 2). Impaired DFV inflow was not related to loss of primary patency in a separate analysis (OR, 2.20; 95% CI, 0.77–6.25; $P = .14$), whereas impaired FV inflow was significantly predictive (OR, 9.74; 95% CI, 2.91–32.58; $P < .001$). The other covariates tested were age (OR, 1.40; 95% CI, 0.53–3.68; $P = .50$), female sex (OR, 2.18; 95% CI, 0.65–7.35; $P = .21$), left-sided stents (OR, 2.00; 95% CI, 0.59–6.78; $P = .27$), stents across the inguinal ligament (OR, 1.96; 95% CI, 0.70–5.46; $P = .20$), length of stents above median of >240 mm (OR, 0.52; 95% CI, 0.19–1.44; $P = .21$), and arterial stents (OR, 0.76; 95% CI, 0.14–4.05; $P = .75$). In a multivariate analysis, only inflow disease of the FV was significantly predictive for loss of primary patency (OR, 10.99; 95% CI, 2.59–46.74; $P = .001$), as shown in Table 3.

Table 2. Univariate binary logistic regression for loss of primary patency within the first year after treatment with venous stents for postthrombotic syndrome.

Variable	Limbs stented for PTS (n=80)*		
	OR	95%CI	P value
Age – above median (>43 y)	1.40	0.53–3.68	.50
Female sex	2.18	0.65–7.35	.21
Left-sided	2.00	0.59–6.78	.27
Stent across IL	1.96	0.70–5.46	.20
Length of stents above median (>240 mm)	0.52	0.19–1.44	.21
Arterial stents	0.76	0.14–4.05	.75
Inflow disease DFV/FV presence vs absence	7.17	2.16–23.78	.001
Inflow disease DFV presence vs absence	2.20	0.77–6.25	.14
Inflow disease FV presence vs absence	9.74	2.91–32.58	<.001

DFV = deep femoral vein; FV = femoral vein; IL = inguinal ligament; OR = odds ratio; PTS = postthrombotic syndrome. * Seven limbs were excluded for length of stents because of missing values.

Table 3. Multivariate binary logistic regression for loss of primary patency within the first year after treatment with venous stents for postthrombotic syndrome.

Variable	Limbs stented for PTS (n=80)*		
	OR	95%CI	P value
Age – above median (>43 y)	1.41	0.43–4.59	.57
Female sex	0.96	0.19–4.99	.96
Left-sided	1.20	0.26–5.58	.81
Stent across IL	1.70	0.44–6.60	.44
Arterial stents	7.15	0.55–93.38	.82
Length of stents above median (> 240 mm)	0.69	0.21–2.31	.55
Inflow disease DFV presence vs absence	0.86	0.23–3.18	.82
Inflow disease FV presence vs absence	10.99	2.59–46.74	.001

DFV = deep femoral vein; FV = femoral vein; IL = inguinal ligament; OR = odds ratio; PTS = postthrombotic syndrome. * Seven limbs were excluded for multivariate analysis because of missing values.

DISCUSSION

This study demonstrated the importance of adequate inflow in patients with PTS undergoing treatment with venous stents. Inflow disease of the DFV and/or FV was present in over half the cohort (54%). Single-vessel FV inflow disease and double-vessel inflow disease increased the risk of primary stent patency loss within the first year; however, secondary stent patency remained high. Primary patency was maintained in single-vessel DFV inflow disease, though the sample size was small ($n = 4$).

Various studies have shown worse patency for stents placed across the inguinal ligament¹⁵, however, with absence of consistent findings across all studies.¹⁶ The authors hypothesize that poor patency in this location is related to inflow disease, rather than the stent's localization. In the current study, primary patency was significantly lower in patients with single-vessel FV and double-vessel inflow disease, who also had stents more frequently placed across the inguinal ligament. Although inflow disease predicted primary patency loss, stent placement across the inguinal ligament was not a significant predictor.

Clinicians may consider avoiding venous stent treatment in the presence of inflow disease; however, the low rate of permanent occlusion (7.5%) within 1 year observed at the authors' center suggests that maintaining stent patency is feasible, even in cases with compromised inflow. High rates of maintained secondary patency are consistent with the 12-month secondary patency (90.4%) of a previous systematic review.³ Three other studies¹⁷⁻¹⁹ have reported an additional loss of primary patency of up to 11.7% and 16% between 1 and 3 years of follow-up after treatment with venous stents for PTS. For 85% of the current cohort ($n = 68$ limbs), long-term primary patency was previously reported and usually maintained after the first year of follow-up.⁴ To maintain patency, sometimes, multiple reinterventions were needed ($n = 15$ limbs) within the first year, with a maximum of 3 reinterventions ($n = 2$ limbs). Strict duplex US follow-up in the current cohort during the first year (at day 1, 2 weeks, 6 weeks, 12 weeks, and 6 months and annually thereafter; using the same protocol after reintervention) allows for early intervention in case of stent obstruction or occlusion, which potentially explains higher long-term patency rates in the previous cohort. Additionally, postprocedural anticoagulant treatment may vary between institutions. The authors hypothesize that maintained stent patency within the first year is crucial for long-term patency; however, this requires future research.

Regarding patient-reported outcomes, the increased risk of reintervention should be discussed with patients before the procedure, to improve deci-

sion making and to set realistic expectations. In a previously published study, 66.2% of the current cohort (n= 45 patients) reported quality of life metrics using the Chronic Venous Insufficiency Quality of Life Questionnaire and the 36-Item Short Form Health Survey.¹⁴ The 36-Item Short Form Health Survey and Chronic Venous Insufficiency Quality of Life Questionnaire findings were similar between patients with and without inflow disease following venous stent treatment; however, poor quality of life was observed after permanent stent occlusion. Therefore, venous stent treatment may be considered for patients with and without inflow disease but should be avoided if a permanent stent occlusion is likely anticipated. Multiple risk factors for reintervention (hematological, technical, and flow-related) should be identified^{4,5}, and a conservative approach should be recommended if permanent stent occlusion is expected. All patients were discussed in a multidisciplinary team before endovenous treatment at the authors' center, with a focus on risk factors for reintervention/occlusion. Less experienced centers may observe different patency rates in limbs with inflow disease and should consider consulting expert centers when inflow is doubtful.

There are several limitations to this study, including the retrospective design, the use of various imaging modalities to score inflow disease, and the limited sample sizes. A minority of limbs (n= 5) could not be included, due to limited availability of imaging to grade DFV/FV inflow. Sample sizes for the subanalysis of single-vessel versus double-vessel inflow disease were small, particularly for single-vessel DFV inflow disease. In addition, diagnostics and treatment are likely to have improved over the years, specifically regarding the visualization of the DFV. Assessment of inflow vessels were subjective assessments in the lack of objective criteria. Although inflow was assessed independent of future outcomes, the authors were not strictly blinded. The different imaging modalities used may have affected the reliability of inflow assessment; however, by using all available imaging, inflow per vessel was scored as accurately as possible using imaging that is also currently used in most centers. Decision making regarding reintervention was also of a subjective nature, due to a current lack of objective standards. According to a Delphi consensus among venous experts, reintervention should be considered for stent stenosis in symptomatic patients or in those with progressive impending in stent failure.²⁰ This approach aligns with decision making in the authors' center. The authors were unable to provide reliable information regarding primary-assisted stent patency because of the lack of these objective criteria and the retrospective study design, including a long study period. A strength is that this study demonstrated a feasible way to identify patients at risk for patency loss due to inflow disease. All available imaging was studied in detail by 3 authors, with disagreements being resolved

after negotiated consensus. This way, an in-depth analysis of the effect of inflow on patency was performed with improved reliability.

Sufficient inflow is important in patients with PTS selected to undergo treatment with venous stents. Single-vessel FV and double-vessel inflow disease showed an increased risk of primary patency loss, although secondary patency was high. Data were too scarce to draw firm conclusions regarding the role of single-vessel DFV inflow disease. While awaiting objective criteria to categorize inflow and consensus among experts in the field of the definition of “sufficient inflow,” the authors encourage other centers to report data on inflow disease in PTS, which will create opportunities for future meta-analyses. Future trials should investigate methods to improve inflow (e.g. by extending stents into inflow vessels or percutaneous transluminal angiography of inflow vessels) and develop predictive models for patency exclusively based on preoperative imaging. Defining criteria for “sufficient inflow” and improving inflow should be priority in deep venous research.

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PART V

EXTRAORDINARY CASES OF DEEP VENOUS DISEASE





Spontaneous Iliac Vein Ruptures: A Systematic Review

(Vascular and Endovascular Surgery, 2023)

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ABSTRACT

INTRODUCTION

Spontaneous iliac vein rupture is a rare, but frequently lethal condition. It is important to timely recognize its clinical features and immediately start adequate treatment. We aimed to increase awareness to clinical features, specific diagnostics, and treatment strategies of spontaneous iliac vein rupture by evaluating the current literature.

METHODS

A systematic search was conducted in EMBASE, Ovid MEDLINE, Cochrane, Web of Science, and Google Scholar from inception until January 23, 2023, without any restrictions. Two reviewers independently screened for eligibility and selected studies describing a spontaneous iliac vein rupture. Patient characteristics, clinical features, diagnostics, treatment strategies, and survival outcomes were collected from included studies.

RESULTS

We included 76 cases (64 studies) from the literature, mostly presenting with left-sided spontaneous iliac vein rupture (96.1%). Patients were predominantly female (84.2%), had a mean age of 61 years, and frequently presented with a concomitant deep vein thrombosis (DVT) (84.2%). After various follow-up times, 77.6% of the patients survived, either after conservative, endovascular, or open treatment. Endovenous or hybrid procedures were frequently performed if the diagnose was made before treatment, and almost all survived. Open treatment was common if the venous rupture was missed, for some cases leading to death.

CONCLUSION

Spontaneous iliac vein rupture is rare and easily missed. The diagnose should at least be considered for middle-aged and elderly females presenting with hemorrhagic shock and concomitant left-sided DVT. There are various treatment strategies for spontaneous iliac vein rupture. An early diagnose brings options for endovenous treatment, which seems to have good survival outcomes based on previously described cases.

INTRODUCTION

Spontaneous causes of retroperitoneal bleeding are easily missed due to its rare entity and uncommon presentation.¹ Spontaneous iliac vein bleeding is such a rare cause, with a poorly understood etiology. Patients mostly present with symptoms and/or signs of a deep vein thrombosis (DVT), but evidence is lacking to prove it as the actual cause of the bleeding.^{2,3} Compression of the left common iliac vein by the right common iliac artery, an anatomical variant called the May-Thurner syndrome (MTS), might explain why spontaneous iliac vein ruptures commonly affect the left side.³

The frequently deadly consequences of a spontaneous iliac vein rupture emphasize the need to raise awareness for the wide clinical presentation, understand its underlying etiology, and learn from previous clinical decisions. The most comprehensive literature review on spontaneous iliac vein rupture was published in 2006 and included 33 patients.³ Many cases of spontaneous iliac vein rupture have been published since and new endovenous treatment techniques have been developed. Improved knowledge on the etiology, clinical presentation, treatment and outcomes of spontaneous iliac vein rupture may help to timely recognize, diagnose, and treat these patients.

This systematic review aims to provide an overview of patient characteristics, etiology, diagnostics, and treatment modalities of spontaneous iliac vein rupture.

METHODS

Protocol

The protocol for this systematic review was entered in the International Prospective Register of Systematic Reviews PROSPERO network (CRD42023392812), and conducted according to the PRISMA statement.⁴

Literature Search

A systematic search was conducted in EMBASE, Ovid MEDLINE, Cochrane, Web of Science, and Google Scholar from inception until January 23, 2023, without any restrictions. A library scientist was consulted to develop the literature search. Terms such as "spontaneous", "unexpected", "non-traumatic", "vein rupture", "tear", and "iliac vein" were included. The complete search strategy is shown in [Appendix A](#).

Study Selection

All English full-text available case reports and case series were reviewed after screening for title and abstract. All studies describing one or more cases of spontaneous iliac vein ruptures and its management were eligible for inclusion, including case-reports, case-series, and reviews. Non-spontaneous iliac vein ruptures, such as trauma, ruptured aneurysm, arteriovenous fistula, complications, and iatrogenic ruptures were excluded. Editorials, letters, comments, and abstract publications were also excluded. Ruptures of other veins than the iliac veins, such as femoral vein, collaterals, or inferior vena cava were also excluded.

The CARE checklist was considered to check the completeness of studies.⁵ References from included review articles were checked manually, and considered for additional inclusion if data was described sufficiently.

Two authors (AK, JB) independently screened studies for eligibility after duplicate removal. Articles were first screened by titles and abstracts, and full-text screened thereafter. Disagreements for study in- and exclusion were resolved by negotiation in which a third reviewer (MR) was involved. The main authors of the studies were contacted if full-text was missing, or data were described insufficient for collection. Study selection was visualized using PRISMA flow diagram for study inclusion.⁴

Data Extraction and Statistics

Data on patient characteristics, clinical presentation, and procedural characteristics were extracted from the included studies and are shown as count with percentages, mean with standard deviation, or median with interquartile ranges. Date of publication and countries where cases came from were also extracted.

RESULTS

Cases

The literature search identified 224 articles after duplicate removal, the complete study selection is shown in [Figure 1](#). Overall, 16 studies were included from a previous literature review. After full-text screening, 76 cases were included in this systematic review presented in 64 studies from all over the world ([Table 1](#)).^{2,3,6-67} Most patients underwent open surgery, the first reported in 1961. Endovenous procedures were reported since 2004. Patient and procedural characteristics are shown in [Table 2](#). Patients were predominantly female (84.2%) with a mean age of 61 years at presentation. The bleeding was mainly located at the left side (96.1%). A concomitant DVT was reported in 84.2% of the patients.

Abdominal pain was the most common complaint during initial presentation (82.9%), but leg swelling (53.9%), back pain (30.3%), and leg pain (31.6%) were also frequently reported, and 67.1% presented with signs of a hemorrhagic shock. Complaints started after physical activity (e.g. bending or walking), recent trauma (e.g. falling from height), defecation, and immobility. Constipation, obesity, previous pelvic surgery, and recent childbirth were also reported as preceding factors.

Figure 1. PRISMA flow diagram for systematic review study inclusion.

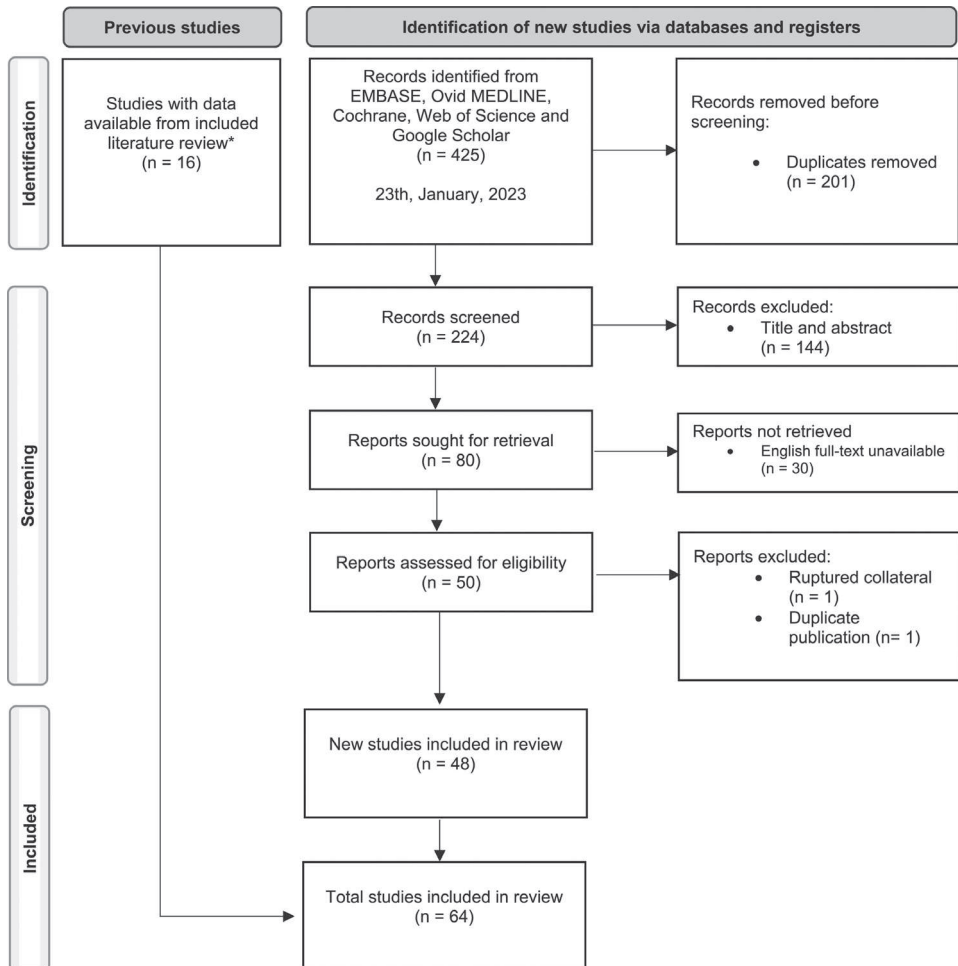


Table 1. Included studies after systematic literature search (1/2)

Study (n= 64)	Country	Case and treatment (n= 76)
Hossne et al. 1961* (6)	Brazil	n= 1, open
Herczeg et al.1967* (7)	Germany	n= 1, open
Herrin et al. 1975* (8)	USA	n= 1, open
Brown et al. 1977 (9)	USA	n= 1, open
McDonald et al. 1980* (10)	USA	n= 1, open
Elliot and Ware 1982 (11)	UK	n= 1, open
Estevan Solano et al. 1982* (12)	Spain	n= 1, open
Noszczyk and Orezko 1983 (13)	Poland	n= 1, open
Stock and Gunn 1986 (14)	UK	n= 1, open
Forsberg et al. 1988 (15)	Sweden	n= 2, open
Copeland et al. 1989* (16)	UK	n= 1, open
Ratia et al. 1989* (17)	Spain	n= 1, open
Hill et al. 1990 (18)	UK	n= 1, open
Arikawa et al. 1992 (19)	Japan	n= 1, open
van Damme et al. 1993* (20)	Belgium	n= 1, open
Nishida et al. 1993* (21)	Japan	n= 1, open
Majeed and Pheils 1993* (22)	UK	n= 1, open
McShannic et al. 1994 (23)	USA	n= 1, open
Yamada et al. 1995 (24)	Japan	n= 1, open
Plate and Qvarfordt 1995* (25)	Sweden	n= 1, open
Lin et al. 1996 (26)	China	n= 1, open
DePass et al. 1998 (27)	Canada	n= 1, open
Lopez-Boado et al. 1998* (28)	Spain	n= 1, open
Gad et al. 1999* (29)	Denmark	n= 1, open
Bracale et al. 1999* (30)	Italy	n= 2, open
Gaschignard et al. 2000 (31)	France	n= 1, open
Pedley et al. 2002* (32)	UK	n= 1, open
Jazayeri et al. 2002 (33)	France	n= 1, open
Tamura et al. 2002 (34)	Japan	n= 1, conservative
Cho et al. 2003 (35)	Korea	n= 1, conservative
Pavon et al. 2003* (36)	Spain	n= 1, open
Kwon et al. 2004 (37)	Korea	n= 1, open
Zieber et al. 2004 (38)	USA	n= 1, endovascular
Yasuga et al. 2004 (39)	Japan	n= 1, open
Tannous et al. 2006 (3)	USA	n= 1, open
Kim et al. 2007 (40)	Korea	n= 1, hybrid
Jiang et al. 2010 (2)	China	n= 3, conservative n= 5, open n= 1, hybrid

Table 1. Included studies after systematic literature search (2/2) (*continued*)

Study (n= 64)	Country	Case and treatment (n= 76)
Zang et al. 2011 (41)	China	n= 1, open
Deng et al. 2011 (42)	China	n= 1, open
Kim et al. 2011 (43)	Korea	n= 1, open
Chen et al. 2013 (44)	China	n= 1, open
Hughes et al. 2013 (45)	USA	n= 1, endovascular
Sadaghianloo et al. 2014 (46)	France	n= 1, open
Kim et al. 2015 (47)	Korea	n= 1, conservative
Pattanshetti et al. 2015 (48)	Indian	n= 1, conservative
Hosn et al. 2016 (49)	USA	n= 1, hybrid
Kalender et al. 2016 (50)	Turkey	n= 1, open
Joseph et al. 2017 (51)	USA	n= 1, open
Chen et al. 2018 (52)	Taiwan	n= 1, hybrid
Ingram et al. 2019 (53)	USA	n= 1, endovascular Δ
Molière et al. 2020 (54)	France	n= 1, conservative
Long et al. 2020 (55)	USA	n= 1, conservative
De Campos Costa et al. 2021 (56)	Portugal	n= 1, open
Sueyoshi et al. 2021 (57)	Japan	n= 1, endovascular
Zheng et al. 2021 (58)	China	n= 2, endovascular
McCready et al. 2021 (59)	USA	n= 1, endovascular n= 1, open
Nishimoto et al. 2021 (60)	Japan	n= 1, endovascular Δ
Ergüneş and Günerhan 2022 (61)	Turkey	n= 1, open
Eziolisa and Chapman 2022 (62)	USA	n= 1, open
Fugaretu et al. 2022 (63)	Romania	n= 1, open
Glengarry et al. 2022 (64)	Australia	n= 1, none
Qi et al. 2022 (65)	China	n= 1, endovascular
Gruter and Oudkerk 2022 (66)	Netherlands	n= 1, hybrid
Huh et al. 2022 (67)	Japan	n= 1, conservative

*= full-text missing, data extracted from Tannous et al.; Δ= initially conservatively treated.

Table 2. Patient characteristics, presentation, type of treatment and survival

Patient characteristics (n= 76)	Outcome
Age, years	61.4 ± 12.2
Female	64 (84.2)
Left-sided	73 (96.1)
Presentation	
Symptoms and signs	64 (84.2), concomitant deep vein thrombosis 63 (82.9), abdominal pain 51 (67.1), hemorrhagic shock 41 (53.9), swollen leg 24 (31.6), leg pain 23 (30.3), back pain 18 (23.7), abdominal mass 6 (7.9), abdominal distension 4 (5.3), leg ischemia 4 (5.3), phlegmasia cerulea dolens
Imaging	46 (60.5), computed tomography 18 (23.7), venography 17 (22.4), ultrasound 1 (1.3), magnetic resonance imaging 9 (11.8), no imaging
Type of intervention (n= 76)	Survived
Conservative/none: n= 12§	9 (75.0)
Open procedures: n= 51	38 (74.5)
· Ligation: n= 13	
· Repair: n= 37	
· Hematoma removal: n= 1	
Endovascular procedures: n= 8	8 (100)
· Coiling: n= 2	
· Thrombectomy and stenting: n= 6	
Hybrid procedures: n= 5	4 (80.0)
· Stenting followed by laparotomy: n= 2	
· Open repair followed by stenting for MTS: n= 3	
<i>Continuous variables presented as mean with standard deviation (SD); categorical variables presented as count (%);§ Thrombolysis started for concomitant DVT, massive bleeding from spontaneous iliac vein rupture, patient died before intervention was possible (Hughes et al, 2013). MTS= May-Thurner Syndrome.</i>	

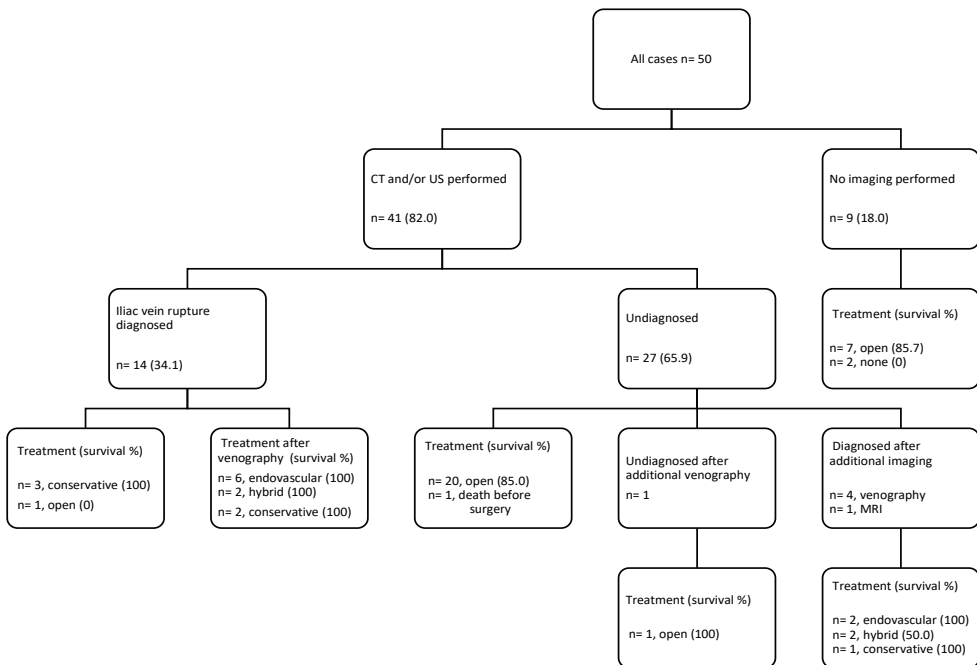
Treatment

Patients underwent either conservative, endovascular, hybrid, or open surgical repair (Table 2). Conservative treatment was suitable for hemodynamically stable patients, including in-hospital monitoring, followed by anticoagulant treatment in case of concomitant DVT. Open, endovascular, or hybrid surgical

procedures were considered for patients with hypovolemic shock, suspicion of active bleeding, or as additional treatment for MTS. Open surgical procedures mostly included primary repair (n= 37, 72.5%), while endovascular treatment consisted of venous stenting or embolization.

Imaging

Data on imaging were available for 50 cases and are shown in [Figure 2](#). In 18.0% (n= 9), no imaging was performed. After ultrasound and/or CT-imaging, an iliac vein rupture remained unrecognized in 65.9% (n= 27). In a subgroup of patients, additional imaging with venography or magnetic resonance imaging (MRI) was performed which then led to the correct diagnose, except for one case in which the rupture was also not diagnosed on the venography.²⁴



Preoperative diagnosis and treatment strategy

In 31 cases (62.0%), the iliac vein rupture remained undiagnosed before start of treatment, even after imaging in some cases ([Figure 2](#)). These patients were all treated conservatively or with open surgery. In 18 of the 19 cases that were adequately identified as having an iliac vein rupture endovenous or hybrid interventions, or conservative treatment was performed. One case underwent open surgery after she suffered a cardiopulmonary arrest, just after the diagnose was made.⁶³

Survival

Overall, 59 patients (77.6%) survived the spontaneous iliac vein rupture and 17 patients died, shown in [Table 2](#). Patients were at least followed until discharge with a maximum follow-up of 50 months. One patient survived the spontaneous iliac vein rupture, but died 7 weeks later of cardiac failure.¹⁵ After open surgery, 38 out of 51 patients survived, while all patients except for one, survived after endovenous or hybrid treatment. One patient died after stent placement, because she developed abdominal compartment syndrome due to the large retroperitoneal hematoma caused by the iliac vein rupture. Laparotomy for abdominal decompression and removal of ischemic intestines was of no avail.⁶⁶

All conservatively treated patients survived except for 2 cases in which the rupture was missed and one case who died before reaching the hospital.⁶⁴ One patient presenting with severe right lower back pain was misdiagnosed with lumbosacral strain and died from cardiac arrest after returning to the ER multiple times.⁵⁵ Another patient received thrombolysis because of an extensive left-sided iliofemoral DVT. In the presence of an iliac vein rupture (conformed during autopsy) the patient started to bleed massively once the thrombus resolved and died before laparotomy could be performed.⁴⁵

Concomitant DVT treatment

A concomitant DVT was reported in 84.2% of the cases, [Table 2](#). Therapeutic anticoagulants were started for 44 out of 64 cases at various times after treatment. The timing ranged from admission, if the patient was hemodynamically stable, towards days after intervention. The duration of the anticoagulant therapy also differed between cases. Heparin, low molecular weight heparin, vitamin-K-antagonist and direct anticoagulants were prescribed. In two cases anticoagulants were not prescribed after conservative management despite a concomitant DVT.^{34,35} Pulmonary embolism was present in four cases.^{14,47,64,67}

DISCUSSION

This is the first systematic literature review of spontaneous iliac vein rupture, describing 76 cases. Spontaneous iliac vein rupture mainly occurs in middle-aged or elderly women, is located predominantly on the left side, often with a concomitant DVT and over half of the cases present with signs of hemorrhagic shock. These ruptures often remain undiagnosed before a treatment strategy is chosen, even after imaging. Undiagnosed patients frequently undergo open surgery, while diagnosed patients are almost always treated with endovascular or hybrid repair.

The overrepresentation of case-reports and case-series in the current literature, emphasize the rare entity of the disease. Increased awareness of symptoms and signs of left-sided DVT, especially in middle-aged or elderly women, may help to early recognize spontaneous iliac vein rupture as the cause of hemorrhagic shock.

Various potential causes of spontaneous iliac vein rupture are hypothesized,³ but its actual etiology is poorly understood. Tannous et al. describe three potential etiologies of a spontaneous iliac vein rupture: mechanical, inflammatory, and hormonal.³ A combination of these factors is thought to explain spontaneous iliac vein rupture by increasing pressure, loss of vessel compliance and weakening of the vessel wall. A common presentation on the left side supports a mechanical cause as a result of compression of the left common iliac vein (MTS), while a concomitant DVT (found in 84%) leads to inflammation of the vessel. The finding that most patients were female and around 60 years-old may support a hormonal cause. While MTS was reported in only 21 patients within our review, the actual prevalence may have been underestimated, since left iliac vein compression is not routinely investigated and imaging was missing for several patients. Also, it is unclear whether the DVT is the cause or the result of the spontaneous iliac vein rupture as external compression from the retroperitoneal hematoma can provoke the DVT.

Timely recognition of spontaneous iliac vein rupture after radiological imaging gives the opportunity to consider endovascular treatment. Endovascular and hybrid procedures for spontaneous iliac vein bleeding reported promising survival rates. In case of concomitant DVT, start of anticoagulant therapy should be considered when the bleeding is stopped. The length of anticoagulant therapy should depend on the cause of DVT, either provoked or unprovoked.⁶⁸ Due to publication bias, especially with case reports, we have to be careful to interpret these findings to optimistically, as less successful cases may remain unpublished. Selection bias may also have affected our findings. Patients that are hemodynamically stable may have had more time to get diagnosed and set-up for endovascular interventions than unstable patients who went straight into the operating room. This most certainly will have affected survival outcomes.

CONCLUSION

Spontaneous iliac vein rupture is rare, but frequently lethal and should be considered as a cause of hemorrhagic shock in patients presenting with a concomitant left-sided DVT, especially in middle-aged and elderly women. It is difficult to diagnose, even with the use of various imaging techniques. Multiple treatment methods are available including conservative, open, endovascular, or hybrid procedures. Timely identification gives the opportunity to consider endovascular treatment.

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APPENDIX A

Spontaneous iliac vein rupture

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	90	89
Embase	Embase.com	1971 - Present	174	91
Web of Science Core Collection*	Web of Knowledge	1975 - Present	61	6
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	0	0
Additional Search Engines: Google Scholar*** (100 top-ranked)			100	45
Total			425	231

***Science Citation Index Expanded** (1975-present) ; **Social Sciences Citation Index** (1975-present) ; **Arts & Humanities Citation Index** (1975-present) ; **Conference Proceedings Citation Index- Science** (1990-present) ; **Conference Proceedings Citation Index- Social Science & Humanities** (1990-present) ; **Emerging Sources Citation Index** (2005-present)

*****Google Scholar** was searched via "Publish or Perish" to download the results in End-Note.

No other database limits were used than those specified in the search strategies

Embase 174

((('vein rupture'/de OR rupture/de) AND ('iliac vein'/de OR 'external iliac vein'/de OR 'common iliac vein'/de)) OR (((spontan* OR idiopath* OR non-traum* OR nontraum* OR unknown* OR unexpect* OR non-iatrogen* OR noniatrogen*) NEAR/12 (iliac* OR ilio* OR femoroili*) NEAR/12 (vein* OR vena OR venous) NEAR/12 (ruptur* OR tear* OR break*))) :ab,ti,kw)

Medline 90

((Rupture/ AND Iliac Vein/) OR (((spontan* OR idiopath* OR non-traum* OR nontraum* OR unknown* OR unexpect* OR non-iatrogen* OR noniatrogen*) ADJ12 (iliac* OR ilio* OR femoroili*) ADJ12 (vein* OR vena OR venous) ADJ12 (ruptur* OR tear* OR break*))) :ab,ti,kf.)

Cochrane 0

(((((spontan* OR idiopath* OR non-traum* OR nontraum* OR unknown* OR unexpect* OR non-iatrogen* OR noniatrogen*) NEAR/12 (iliac* OR ilio* OR

femoroili*) NEAR/12 (vein* OR vena OR venous) NEAR/12 (ruptur* OR tear* OR break*))):ab,ti,kw)

Web of Science 61

TS=((((spontan* OR idiopath* OR non-traum* OR nontraum* OR unknown* OR unexpect* OR non-iatrogen* OR noniatrogen*) NEAR/12 (iliac* OR ilio* OR femoroili*) NEAR/12 (vein* OR vena OR venous) NEAR/12 (ruptur* OR tear* OR break*)))))

Google Scholar

"spontaneous|idiopathic|unexpected iliac vein rupture"|"spontaneous|idiopathic|unexpected rupture**iliac vein"|"spontaneous|idiopathic|unexpected**iliac vein rupture" 'spontaneous|idiopathic|unexpected iliac vein rupture'|spontaneous|idiopathic|unexpected rupture**iliac vein'|spontaneous|idiopathic|unexpected**iliac vein rupture'





Spontaneous retroperitoneal hematoma

(Klinische praktijk: Spontaan retroperitoneaal hematoom, Nederlands Tijdschrift voor Geneeskunde, 2024; English Translated)

**Bakas JM, Kooiman AL, van Rijn MJE. [Spontaneous retroperitoneal hematoma].
Spontaan retroperitoneaal hematoom. Ned Tijdschr Geneeskd. 2024;168**

SUMMARY

Spontaneous retroperitoneal hematoma refers to bleeding of the retroperitoneal space without prior trauma or iatrogenic injury. Its diagnosis is often delayed due to an uncommon clinical presentation. This case-series presents three patients with spontaneous retroperitoneal bleeding. Patient A presented with a spontaneous bleeding around the right iliopsoas muscle due to antiplatelet medication and was managed conservatively. Patient B had a spontaneous arterial bleeding near the right kidney, subsequently determined to be associated with a pheochromocytoma. Endovascular treatment successfully stopped the bleeding. The pheochromocytoma was resected during follow-up. Patient C had a spontaneous rupture of the left iliac vein with a concomitant deep vein thrombosis. She underwent emergent laparotomy, but unfortunately did not survive. This case-series emphasize the diverse presentation, varied causes, and different treatment strategies for spontaneous retroperitoneal hematoma. Timely diagnosis is hard, but crucial to enable an individualized treatment.

Dear colleagues, a retroperitoneal bleeding might appear after trauma or iatrogenic injury, or even spontaneously without any clear bleeding cause. This case-series emphasize that it might be challenging to identify spontaneous causes for retroperitoneal bleeding.

Patient A is a 71-year-old man who underwent coronary artery bypass graft (CABG) in the past and previously suffered a transient ischemic attack (TIA). He was set on antithrombotic management (carbasalate calcium), because of his medical history. Currently, the patient underwent treatment for erysipelas of the right lower limb. During this treatment, he suddenly developed right inguinal pain, with muscle weakness and numbness of the right lower limb. His right limb was swollen, but not strained or severely painful. A CT-scan with intravenous contrast revealed a retroperitoneal hematoma around the right iliopsoas muscle, without signs of active bleeding. Patient A underwent a conservative treatment, because of the hemodynamically stable condition. The hemoglobin values decreased from 8.0 to 5.5 mmol/L (reference: 8.5 – 10.5). A second CT-scan was performed the next day, because of hypotension and decreased diuresis. At this time, an active bleeding was visualised, however, still without a clear bleeding focus ([Figure 1](#)).

Figure 1 Retroperitoneal hematoma around the right iliopsoas muscle in patient A: Axial CT-scan with intravenous contrast (arterial phase) of the abdomen in a 71-year-old patient with cardiovascular medical history, treated because of erysipelas of the right lower limb. The CT-scan was performed because of sudden right inguinal pain, with numbness and muscle weakness of the right lower limb. A retroperitoneal hematoma was visualized around the right iliopsoas muscle, with active bleeding.



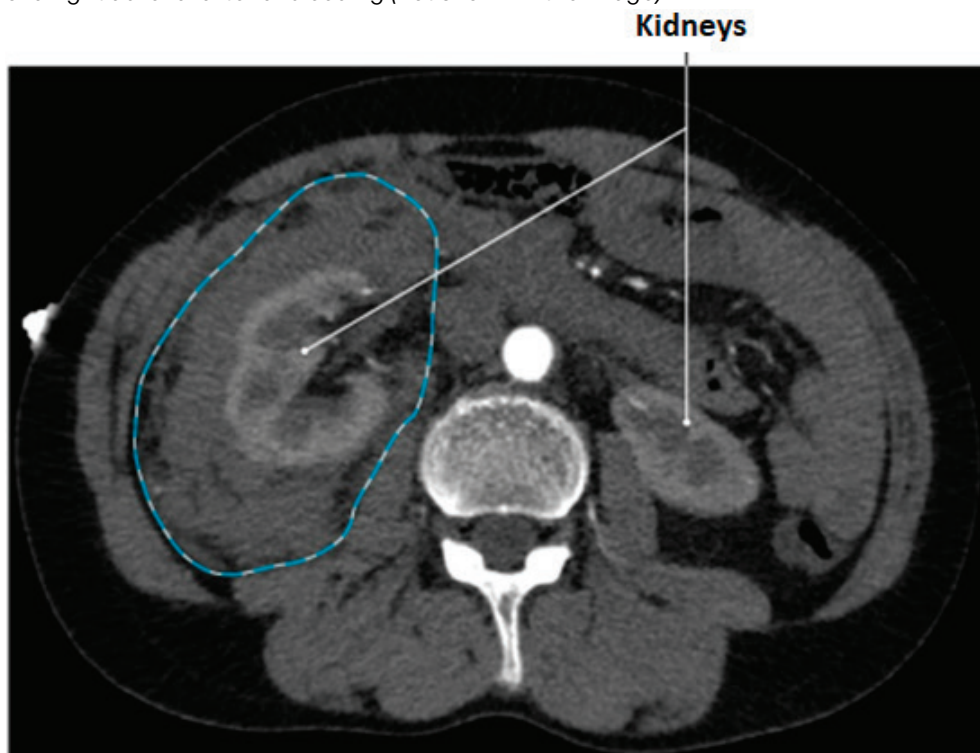
6B

Patient A was transferred to our hospital for further management. Three packed cells were administered at arrival. The patient was responsive and hemodynamically stable (blood pressure 119/79 mmHg, pulse 95/min). The right lower quadrant of the abdomen was swollen and painful during clinical examination. We performed an angiography to localize any bleeding focus, which also gave the opportunity for immediate embolization (if necessary). Again conservative treatment was chosen, because of a presumably tamponed bleeding. The same evening the patient collapsed while standing up, without losing consciousness. Laboratory testing revealed a Hb of 4.5 mmol/L, therefore, two packed cells and tranexamic acid were administered; the next day one additional packed cell was administered. After this event, the patient remained clinically stable and also recovered from his erysipelas. The fourth day of hospitalization, he was trans-

ferred back to the referring hospital in a clinically stable condition with Hb 5.3 mmol/L.

Patient B, a 48-year-old man, without relevant medical conditions, presented at the emergency room (ER) of another hospital with nausea, vomiting, and a continuous sharp right flank pain. The pain had started suddenly several hours ago. Patient B had no fever, no urinary tract symptoms and defecation was normal. Clinical examination revealed a tense abdomen, with a painful right flank and hemi-abdomen. A CT-scan with intravenous contrast revealed a right adrenal arterial bleeding ([Figure 2](#)). As a result, the patient was transferred to our institution for further management. The patient was pale and transpiring, with a blood pressure of 144/103 mmHg and a pulse of 124/min. The Hb was 6.3 mmol/l.

Figure 2 Retroperitoneal hematoma around the right kidney in patient B: Axial CT-scan of the abdomen with intravenous (arterial) contrast in a 48-year-old patient, without relevant medical conditions, presenting with severe sharp right flank pain, nausea, and vomiting. A retroperitoneal hematoma is shown around the right kidney. This was a result of a right adrenal arterial bleeding (not shown in the image)



We additionally performed an angiography under anaesthesiology to detect any focus for bleeding. An active bleeding was revealed around the right adrenal region, suspected for a kidney tumour. The right adrenal artery was embolized and the distal part of the right phrenic artery as well. After successful intervention, the patient remained hemodynamically stable. The Hb levels were decreased to 4.7 mmol/L, with increased cardiac markers in the blood. Two packed cells were administered, and the Hb levels remained above 6.0 mmol/L thereafter. Increased cardiac markers, were suspected to be caused by hypovolemic shock and concomitant mismatched myocardial oxygen supply and demand (type II ischemia). Ten days after discharge, the patient was readmitted because of a recurrent episode of sudden right flank pain. No bleeding was revealed after CT-imaging. Pain medication was optimized during admission, and the patient was discharged in stable condition.

A kidney or adrenal tumour was suspected to be the bleeding cause in this patient, such as an adenoma, pheochromocytoma or carcinoma. Increased plasma concentration of normetanephrine was detected, which were possibly explained by the presence of a pheochromocytoma or by stress (false-positive). A PET-scan at the outpatient clinic confirmed the diagnose pheochromocytoma. The patient underwent a laparoscopic right adrenal 'en bloc'-resection. Because of fibrosis and peri-tumoral inflammation, the procedure was converted to open surgery.

Patient C, a 71-year-old woman, without relevant medical conditions, suddenly experienced light-headedness, headache, and lower backpain. Short thereafter she lost consciousness, and out of hospital resuscitation was started. The patient had already been intubated during arrival at the ER. She remained hypotensive, despite administering fluids, blood products, atropine and adrenalin. The pulse was 40 beats/min, temperature 33,4 °C, and Hb 3.3 mmol/L. Clinical examination revealed a marbled skin, normal abdomen, palpable inguinal pulsations, with a swollen left lower limb. A CT-scan with contrast revealed an extensive retroperitoneal hematoma around the left kidney, without extravasation of contrast. The cardiac arrest was presumable caused by a haemorrhagic shock, possibly due to a bleeding kidney tumour. Conservative treatment would result in a fast decline of hemodynamic parameters and a palliative prognosis. In the absence of possibilities for endovascular treatment, the medical team decided for an open surgical approach.

The vascular surgeon and urologist performed the surgical procedure. The swollen left lower limb, was initially suspected to be caused by left iliac vein compression due to the hematoma. The retroperitoneal space was opened and

the abdominal aorta was clamped during the procedure. Surgical exploration revealed a lacerated left ovarian vein at the level of the left renal vein, presumably due to traction caused by the hematoma. The vein was ligated and the renal vein was sutured, with a consequent left-sided nephrectomy in order to stop the presumed bleeding cause.

Macroscopic examination revealed a small space-occupying lesion of the left kidney, without signs of bleeding. The interventional radiologist had re-examined the computed tomography and informed the operating team that the left iliac vein seemed to be ruptured. Further surgical exploration indeed revealed a ruptured left external iliac vein. The rupture was sutured and the abdominal cavity was packed with gauzes. Subsequently, the blood pressure decreased after attempt to remove the aortic clamps. The patient passed away before arrival at the intensive care unit, despite multiple attempts to stabilize the patient. Obduction revealed status after left-sided nephrectomy, retroperitoneal and intraperitoneal hematoma, with sutures in the left renal vein and left ovarian vein. The surrounding tissue of the iliac vein revealed a hematoma extending to the left lower limb. A ruptured iliac vein was also identified, where the sutures were present. Also a thrombus was identified in the left internal and external iliac veins. Microscopic examination identified organizing thrombi in the left internal, external and common iliac vein, with granulation and revascularisation near the edges.

Because of the presence of thrombi during clinical obduction, a deep vein thrombosis (DVT) was mentioned as a possible cause of iliac vein rupture. A spontaneous rupture of the left iliac vein is most often present in patients with a DVT.⁹ Both clinical and radiological signs of DVT, were present in patient C.

CONSIDERATION

Three patients with spontaneous retroperitoneal hematoma were described in this article. The cases showed that the treatment depends on the presence of an active bleeding focus, and that the treatment depends on the aetiology and presence of any active bleeding focus.¹ Furthermore, the cases confirm the atypical and diverse clinical presentation of spontaneous retroperitoneal hematoma, which could result in a delayed diagnose.² The diverse clinical presentation of retroperitoneal hematoma, aetiology, and treatment methods, is further illustrated below.

Spontaneous retroperitoneal bleeding

There are various potential causes of a spontaneous retroperitoneal bleeding, with approximately two-thirds related to anticoagulant therapy.³ Other causes are often rare, such as tumours, gynaecological abnormalities, and spontaneous venous bleeding. The clinical presentation is also diverse: approximately two-thirds of patients present with abdominal pain, around 20% with backpain or lower limb pain, and less than 10% with a palpable abdominal mass or skin alteration (abdomen, back, or flank). The presentation might be acute with signs of haemorrhagic shock, or subacute with misunderstood anaemia and abdominal pain.^{1,3} The diagnose could be confirmed after CT-scan of the abdomen with intravenous contrast (plain/non-contrast, arterial contrast, and venous contrast). The treatment is often conservative.⁴ The precise incidence of spontaneous retroperitoneal hematoma is unknown. The condition is rare; previous studies mainly included case-reports, case-series, or small retrospective cohort studies.²⁻⁵

Anticoagulant therapy

Above two-thirds of spontaneous retroperitoneal hematoma affects patients with concomitant use of anticoagulant therapy.^{2,3} Bleeding could start during treatment with anticoagulant therapy, such as vitamin-K-antagonists, low-molecular-weight heparin, and direct-oral anticoagulants, but also during use of platelet inhibitors.³⁻⁵ The conservative treatment of spontaneous retroperitoneal hematoma includes clinical observation (hospital admission), controlled hemodynamic (blood products), and reversing anticoagulant effects.^{2,5} Eleven patients died after a spontaneous retroperitoneal hematoma in a previous study, the bleeding was presumed to be adequately "controlled" in five patients.² The last patients did not directly die as a result of the hematoma, but due to other (indirect) causes, such as aspiration-pneumonia, cardiovascular diseases, or cerebrovascular accident.² It seems likely, that these lethal cases were rather related to patient frailty.

Arterial bleeding

Various retroperitoneal structures may bleed. A known common source of acute retroperitoneal bleeding is a ruptured abdominal aortic aneurysm, however these are not strictly considered a "spontaneous" bleeding source in the literature.^{2,3} Bleeding from retroperitoneal arteries is less common.⁶ A CT-scan of the abdomen with intravenous contrast helps to identify the bleeding source and extension. Also, whether an active bleeding is present could be identified (contrast extravasation). The bleeding localization helps to identify the aetiology, the extension helps to identify the estimated loss of blood, and the presence of contrast extravasation helps to decide an appropriate treatment strategy.

An endovascular procedure is minimal invasive and therefore preferred. Open-surgical procedures could be considered in the lack of endovascular treatment options, during persisting hemodynamic instability or suspected abdominal compartment syndrome.^{4,7}

Spontaneous iliac vein ruptures

Multiple theories exist for the aetiology of spontaneous iliac vein ruptures: mechanical, inflammatory, and hormonal.⁸ The mechanical hypothesis is related to the May-Thurner syndrome. This syndrome involves increased venous pressure of the left lower limb and pelvis, due to a compressed left common iliac vein between the overlying right common iliac artery and the fifth lumbar spine. The inflammatory hypothesis presumes that the likelihood for rupture increases, because of lost vessel wall elasticity due to chronic inflammation following DVT. The hormonal hypothesis presumes that oestrogen prevents against vessel wall rupture. The literature reveals 76 patients with spontaneous iliac vein ruptures, in 64 studies.⁹ Around 96% of the patients had a left-sided rupture, 84% was a female patient, and 84% had a concomitant DVT. The mean age was 61 year. A spontaneous iliac vein rupture should therefore be considered in case of left-sided retroperitoneal bleeding with concomitant DVT, especially in middle-aged (or elderly) female patients. For 62% of the patients, the diagnose was unknown after imaging, but was made during treatment.⁹ When a venous cause of retroperitoneal hematoma is suspected, An open-surgical approach should not be preferred for venous causes of retroperitoneal hematoma, especially when the bleeding focus is unclear, unless for an utmost effort in a case between life or death. The table shows an overview of causes of spontaneous retroperitoneal hematoma and treatment methods to consider. However, each case of spontaneous retroperitoneal hematoma is unique and deserves an optimized treatment.

Table: Common causes of spontaneous retroperitoneal hematoma, with treatment strategies *

cause	treatment strategy		
	non-invasive	minimal invasive	invasive
medicinal	- cessation of anticoagulant therapy, if possible reverse the effects of anticoagulant therapy - tranexamic acid - controlled haemodynamics	- endovascular embolization in case of active bleeding source	- open-surgical exploration to clear out the hematoma Φ
spontaneous arterial or venous bleeding #	- tranexamic acid - controlled haemodynamics	- endovascular embolization or treatment with covered stents in case of active bleeding source	- open-surgical approach of the bleeding focus for sutures or ligation Φ
spontaneous bleeding from an organ or tumour	- tranexamic acid - controlled haemodynamics	- endovascular embolization in case of active bleeding source	- open-surgical resection of the bleeding tumour or affected organ, or ligation or sutures at the bleeding focus §

* The table illustrates a global overview. Multiple concomitant causes might be present in spontaneous retroperitoneal hematoma, such as medicinal causes combined with spontaneous venous bleeding.

± Related to anticoagulant therapy

Φ Rarely indicated

Such as a ruptured iliac vein

§ If applicable

Dear colleagues, this article illustrates the diverse clinical presentation of spontaneous retroperitoneal hematoma, the diversity in aetiology, and the various potential treatment methods. Also after appropriate imaging, it might be challenging to identify the underlying cause of spontaneous retroperitoneal hematoma. A timely diagnose is important to offer an optimized treatment. Treatment methods may include either conservative, endovascular, or open-surgical treatment.

HIGHLIGHTS

- Spontaneous retroperitoneal bleeding is a non-traumatic bleeding.
- Clinical presentation, aetiology, and treatment methods are diverse.
- The diagnosis should be considered in case of vague abdominal complaints with a misunderstood anaemia.
- Spontaneous retroperitoneal hematoma is a challenging diagnose, even after adequate imaging.
- Timely recognition of the underlying cause is important to consider appropriate treatment strategy: conservative, endovascular, or open-surgical.

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Exercise Intolerance That Resolved After venous Stenting of the Inferior Vena Cava

(Vascular and Endovascular Surgery, 2023)

Bakas JM, Moelker A, Malskat WSJ, Van Rijn MJE. Exercise Intolerance That Resolved After venous Stenting of the Inferior Vena Cava. Vascular and Endovascular Surgery. 2024 Jan;58(1):100-104. Epub 2023 Jul 5. doi: 10.1177/15385744231188801

ABSTRACT

Venous stenting could alleviate exercise intolerance associated with chronic inferior vena cava (IVC) obstruction. We describe a 36-year-old male patient with an unknown IVC-obstruction. The obstruction was discovered after a bi-iliac deep vein thrombosis (DVT). The thrombus was resolved using thrombolysis. In the chronic phase, the patient developed exercise intolerance without any leg-specific symptoms or signs. Venous stenting was performed to open the IVC-obstruction, 1 year after the acute DVT. His physical condition improved, but cardiac magnetic resonance imaging at rest did not reveal hemodynamical changes after stenting. The Short Form Health Survey (SF-36) physical and mental component summaries were increased from 40.3 to 46.1 and 42.2 to 53.7, respectively. In patients with ilio caval obstruction, improved venous flow without changes in resting hemodynamics can enhance exercise intolerance and quality of life, even in the absence of leg symptoms. Diagnostic tools performed only at rest may miss abnormalities.

INTRODUCTION

Partial or complete inferior vena cava (IVC) obstruction has a prevalence around 0.15%.¹ It is often referred to as a congenital disorder, but may also result from thrombotic events in early childhood.² Assessment of IVC-anomalies, including hypoplasia or aplasia is needed in DVT patients, especially those with iliofemoral DVT.³ Young patients with chronic IVC-obstruction may present asymptomatic, but are at risk for acute deep vein thrombosis (DVT), presenting at a mean age of twenty-five.² Patients tend to develop post-thrombotic syndrome (PTS) later in life, which may cause pain, swelling, and/or ulceration of the leg.⁴ Exercise intolerance including dyspnea, exhaustion and turning pale during physical activities, is also observed.²

Deep venous stenting is an accepted treatment for symptomatic iliofemoral obstruction,⁵ but evidence is limited supporting its use for exercise intolerance. Endovenous recanalization, followed by venous stenting, could relieve exercise intolerance in IVC-obstruction.⁶ Cardiorespiratory functioning tests can be used to evaluate exercise intolerance in IVC-obstruction and its response to treatment.⁷ However, the impact of treatment on hemodynamics and quality of life (QoL) is unclear. Venous blood return is altered in IVC-obstruction, with the azygos vein, ascending lumbar veins, and abundant communicating veins becoming more prominent.⁸ Venous recanalization presumably resolves exercise intolerance by enhanced venous blood return.

This case-report presents a patient with exercise intolerance due to IVC-obstruction, which was accidentally discovered at presentation with an acute iliofemoral DVT. One year following acute DVT, the patient underwent venous stenting. Hemodynamics, clinical features, and quality of life (QoL) were evaluated pre- and post-procedure. Informed consent was obtained from the individual described in this case-report.

CASE PRESENTATION

Acute Phase

A 36-year-old male patient was referred to our academic hospital for endovenous treatment of acute bi-iliac DVT with coincidental finding of IVC-obstruction. One week earlier, he was admitted for ilio caval DVT and treated conservatively with a heparin pump elsewhere, subsequently replaced with a direct-oral-anticoagulant. He experienced minimal back pain and bilateral in-

guinal pain at discharge. However, he was readmitted after 3 days due to worsening of complaints.

Upon arrival at our institution, the patient had a fever, malaise, back pain, severe bilateral groin pain, and impaired mobility. Notably, leg symptoms and/or signs were absent. Duplex ultrasound (DUS) and Computed tomography venography (CTV) revealed an extensive DVT from the femoral veins above the knee until the IVC, including a thrombosed collateral vein (Figure 1a.). From the collateral vein upwards, the IVC demonstrated a small lumen, extending to the level of the hepatic veins.

Figure 1. Computed tomography venography before thrombolysis (a); after thrombolysis (b); after venous stenting (c).



Thrombolysis successfully restored patency of both iliac veins and the most distal segment of the IVC, but was stopped due to bleeding complications before the collateral opened (Figure 1b.). Recanalization of the chronic IVC-obstruction was initially waived, because most symptoms had resolved.

Chronic Phase

During the 6-month-control, the patient reported exercise intolerance. His complaints consisted of reduced physical condition, dyspnea, exhaustion and paleness during physical activities such as walking and cycling, without any leg-specific symptoms or signs. These complaints were absent prior to his acute DVT. Duplex ultrasound and CTV revealed a re-occlusion of the common iliac veins and distal IVC, with patent external iliac, femoral, and popliteal veins.

Venous stenting was planned to improve cardiac preload and to resolve complaints. Cardiac magnetic resonance imaging (MRI) and the Short Form Health Survey (SF-36) questionnaire were used to evaluate the effect, both pre- and post-procedure.

Procedure

The first attempt of recanalization failed, but in a second attempt, the IVC was successfully stented. Both femoral veins and the right jugular vein were punctured for access. The IVC was recanalized after a snaring procedure creating a through and through wire. Intravascular ultrasound (IVUS) determined stent position and length after percutaneous transluminal angioplasty (24 mm for IVC, 16 mm for iliac veins). The IVC was stented right below the hepatic veins with 3 SinusXL (OptiMed®, Ettlingen, Germany) overlapping stents (80 × 24 mm + 80 × 24 mm + 16 × 24 mm), in which two BeYond (Bentley®, Hechingen, Germany) stents (16 × 150 mm) were placed in a kissing fashion extending into the external iliac veins, with one additional stent (16 × 120 mm) on the right side.

Outpatient Clinic

Figure 1c. shows patent venous stents without signs of complications. The patient received low-molecular-weight heparin and was discharged the next day. Anticoagulation was switched to a vitamin-K-antagonist after 2 weeks. Duplex ultrasound revealed patent venous stents until date (current follow-up 6 months). The patients' physical condition improved, allowing him to exercise (daily activities, walking and cycling) without dyspnea, dizziness, or paleness. He also felt fitter during the day.

Heart Volumes

Table 1 shows end-diastolic volume (EDV), end-systolic volume (ESV), systolic volume (SV), ejection fraction (EF), and 2D-flow measures of the cardiac valves. Heart volumes were similar before and after venous stenting at rest, and the forward stroke volume of the aortic, pulmonic, and atrioventricular valves aligned with these results.

Table 1. Cardiac magnetic resonance imaging (MRI), including 2D flow and heart volumes before and after deep venous stenting.

Left ventricle	Before stenting	After stenting + 2months
MRI measures		
EDV (mL/m2)	99	94
ESV (mL/m2)	39	40
SV (mL/m2)	60	54
EF (%)	60	57
Right ventricle		
EDV (mL/m2)	100	96
ESV (mL/m2)	41	41
SV (mL/m2)	60	55
EF (%)	60	57
Forward stroke volume		
Aortic valve (mL/beat)	126	123
Mitral valve (mL/beat)	113	138
Pulmonic valve (mL/beat)	117	120
Tricuspidal valve (mL/beat)	106	120

LV: left ventricle, RV: right ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; SV: systolic volume; EF: ejection fraction

Table 2. Quality of life before and after deep venous stenting.

SF-36 domains (0-100)	Before stenting	+3 months after stenting	Dutch population (35-44 years old)
Physical Functioning	85.0	90.0	90.0
Role-Physical	25.0	75.0	82.9
Bodily Pain	74.0	74.0	83.8
General Health	25.0	52.0	74.0
Vitality	50.0	70.0	67.1
Social Functioning	50.0	75.0	88.0
Role-Emotional	33.3	100.0	82.2
Mental Health	80.0	80.0	76.9
Physical Component Summary	40.3	46.1	NR
Mental Component Summary	42.2	53.7	NR

A higher SF-36 score indicating a better quality of life (0-100); Age-adjusted SF-36 outcomes of the general Dutch cohort were extracted from van der Zee et al. (1993); NR= not reported

Table 2 shows the SF-36 before and 3 months after venous stenting, with reference values of an age-adjusted Dutch cohort.² The SF-36 is divided in physical functioning, role limitations due to physical health (role-physical), bodily pain, general health, vitality, social functioning, role limitation due to emotional problems (role-emotional), and mental health.¹⁰ Each domain scores between 0 and 100, with higher scores indicating a better QoL. Domains are summarized in a mental and physical component summary.

All SF-36 domains remained stable or increased after venous stenting. Disabilities before the procedure were common in the role-physical, general health, and role-emotional domains with increased mean differences between 27.0 and 76.7 post-procedure. Physical and mental component summary also increased with 5.8 and 11.5 points, respectively.

DISCUSSION

We presented a young male patient with exercise intolerance due to ilio caval obstruction. Endovenous recanalization followed by venous stenting led to complete resolution of his symptoms 1 year after the initial DVT. His SF-36 scores increased and were comparable to those of an age-matched Dutch cohort. However, there were no changes in heart volumes at rest before and after venous stenting.

Exercise intolerance is often underestimated as a consequence of chronic (ilio)caval obstruction.¹¹ It is not regularly evaluated in venous outflow obstruction.¹² Currently, exercise intolerance also is not included in any PTS score. Inadequate return of venous blood to the heart may cause exercise intolerance. Reduced venous return from the lower limbs during exercise reduces stroke volume and cardiac output in ilio caval outflow obstruction.¹¹ Venous stenting presumably resolves exercise intolerance, by enhancing venous return and increasing cardiac output.

Evaluating cardiac hemodynamics at rest may fail to detect venous abnormalities, as resting venous capacitance may not reveal the increased demands of venous volume during exercise.¹¹ Despite unchanged pre- and post-venous stenting heart volumes, that were within the normal range, our patient experienced an improvement, as evidenced by SF-36 scores. Cardiac volumes were also normal at rest in patients with exercise intolerance after IVC-ligation, while lower volumes were measured during exercise.¹³ Therefore, diagnostic tools may miss abnormalities if only performed at rest.

Another lesson learned is that in acute DVT resulting from chronic IVC-obstruction, the IVC may be left untreated, with only fresh clot removal followed by lifelong treatment with anticoagulants. However, if collateral vessels remain occluded, persisting symptoms and signs may necessitate invasive treatment during follow-up.

CONCLUSION

This case increases awareness for symptoms and signs related to physical exercise in venous ilio caval obstruction. Future studies are needed to reveal how venous stenting affects hemodynamics during exercise in IVC-obstruction. Understanding the impact of venous stents on cardiac hemodynamics and exercise-related complaints, may improve treatment selection for IVC-obstruction.

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A Case of Complete Resolution of Cauda Equina Syndrome Caused by Extensive Iliocaval Thrombosis: The Role of Thrombolysis and Venous Stents

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ABSTRACT

PURPOSE

The cauda equina syndrome (CES) is a rare condition affecting less than 1 in 100,000 patients annually. Diagnosing CES is challenging because of its rare incidence, potentially subtle presentation, and various underlying etiologies. Vascular causes, such as inferior vena cava (IVC) thrombosis, are uncommon but should be considered, since timely recognition and treatment of deep vein thrombosis (DVT) as a cause of CES can avoid irreversible neurological damage.

CASE REPORT

A 30-year-old male presented with partial CES caused by nerve root compression due to venous congestion from an extensive ilio caval DVT. He completely recovered after thrombolysis and stenting of the IVC. His ilio caval tract remained patent until the last date of follow-up at 1 year without signs of post-thrombotic syndrome. Broad molecular, infectious, and hematological laboratory tests did not reveal any underlying disease for the thrombotic event, particularly no hereditary or acquired thrombophilia.

CONCLUSION

Timely recognition of venous thrombosis as a cause of CES is essential. This is the first case report of CES caused by an extensive ilio caval DVT successfully treated with thrombolysis and venous stenting with good resolution of DVT and CES.

CLINICAL IMPACT

This case-report describes a patient with cauda equina syndrome resulting from an extensive ilio caval deep vein thrombosis due to an underlying stenosis of the inferior vena cava. Thrombolysis and venous stenting successfully restored venous patency and thereby relieved symptoms and signs of cauda equina syndrome, in addition to (long-term) therapeutic dose anticoagulation. It is important to timely recognize deep vein thrombosis as a cause of cauda equina syndrome and to consider endovenous treatment in a specialized center.

INTRODUCTION

The cauda equina syndrome (CES) is a rare condition affecting less than 1 in 100,000 patients annually.¹ Symptoms and signs of CES, such as sciatica, loss of urinary function, and altered saddle sensation can be challenging to recognize, because of the occasionally subtle presentation.² There are various etiologies of CES such as disk herniation, tumors, infection, spinal stenosis, and inflammatory disease.³ A timely diagnosis and adequate treatment of the underlying cause is important to avoid severe irreversible neurological damage.⁴

Although uncommon, vascular causes of CES have been described and should not be overlooked.³ Epidural vein engorgement has been revealed by magnetic resonance imaging (MRI) in patients with deep vein thrombosis (DVT) or compression of the IVC, causing a radicular syndrome by spinal cord or nerve root compression.⁵ So far, three cases of CES caused by IVC thrombosis or obstruction have been reported: one IVC thrombosis was treated with anticoagulants only,⁶ another IVC thrombosis with thrombectomy and thrombolysis,⁷ and a case of IVC atresia was treated by open surgical nerve root decompression.⁸ Treatment of CES with a venous stent has only been reported once for a patient with left common iliac vein compression.⁹

Deep venous stenting is increasingly performed for occlusion or atresia of the IVC in patients with symptoms and signs of the post-thrombotic syndrome (PTS),¹⁰ but has never been described in the context of treating CES. We describe a case of CES resulting from an extensive ilio caval DVT due to an underlying stenosis of the IVC, successfully treated with thrombolysis and stenting. Informed consent was obtained from the individual described in this case-report.

CASE REPORT

Presentation

A 30-year-old male initially presented at a local hospital with progressive complaints of back pain and swollen legs for 4 days. He had no relevant medical history besides a pyloromyotomy and orchidopexy as a child. He was able to walk, but his legs felt heavy and numb. Defecation was absent for 2 days and urinary miction was difficult, but still possible. He had no cardiac or respiratory complaints. His body mass index was 26.3 kg/m², he was a current smoker for 10 years, and did not use any medication.

Examination

Both legs of the patient were red and swollen, with intact motor functions. He had an altered saddle sensation with numbness around the anus, a lowered sphincter tension, and a lowered anal reflex. Plantar reflexes of the feet were indifferent on both sides. The femoral, popliteal, tibial posterior, and dorsalis pedis pulses were all palpable bilaterally. His clinical presentation was suggestive for an incomplete CES.¹¹

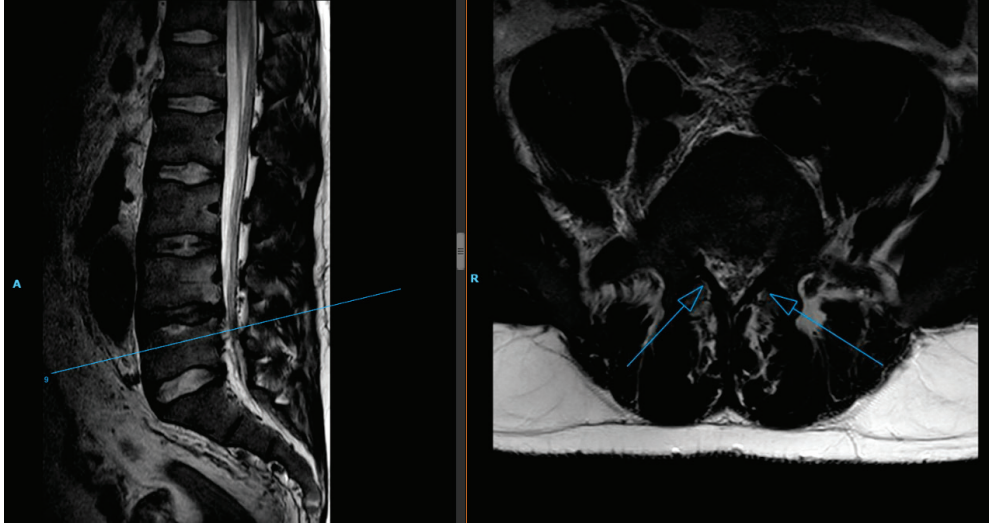
Computed tomography angiography (CTa) showed an extensive thrombus in the IVC and left and right common and external iliac veins, as shown in [Figure 1](#). Collaterals at the level of the renal veins were indicative of a chronic stenosis of the IVC. Coincidental findings were a mild splenomegaly and a small abnormality around the pyelum of the right kidney.

Direct nerve root compression due to venous congestion was revealed on MRI with decreased venous outflow of the nerve roots itself, shown in [Figure 2](#). Cerebrospinal fluid was missing around the nerve roots of L4-L5, possibly because of epidural lipomatosis combined with mild bulging of the lumbar disk and congestion of the venous plexus leading to enlarged epidural veins.

Figure 1. Computed tomography angiography showing extensive ilio caval thrombosis at the emergency room (left), and patent inferior vena cava 3 months after deep venous stenting (right).



Figure 2. Magnetic resonance imaging during presentation at the emergency room.



Sagittal imaging of the spine shown on the image (left). Venous congestion at the level of L4-L5 indicated by open arrow on axial imaging (right).

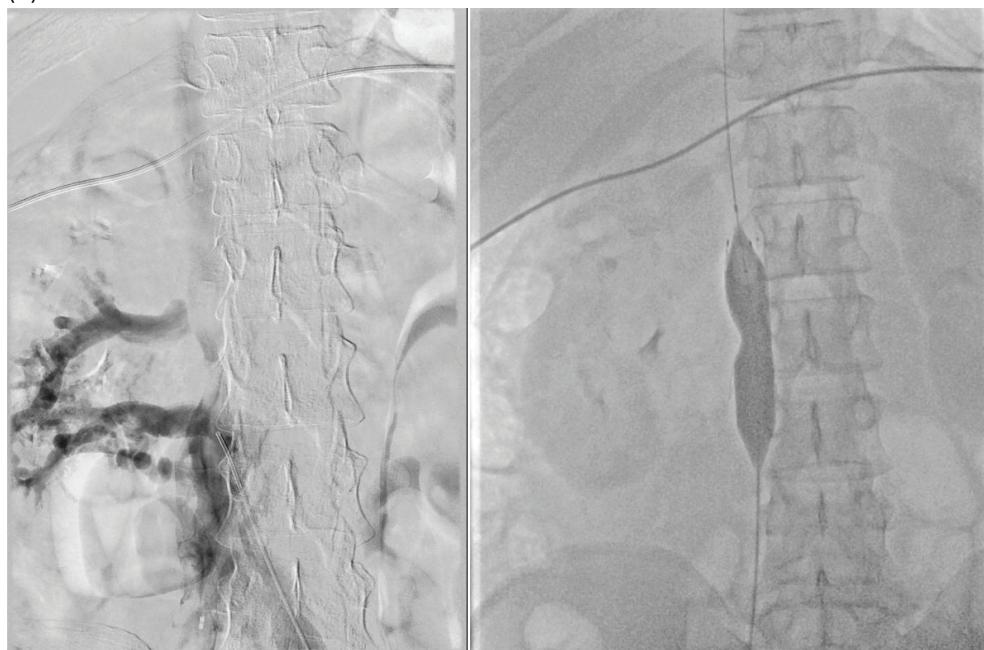
Medical specialists of the department of vascular surgery, neurology, neurosurgery, hematology, and (interventional) radiology were involved. Based on the clinical findings and findings on CTa and MRI, the most likely cause of CES was the ilio caval DVT. The patient started therapeutic anticoagulation with intravenous unfractionated heparin and was referred to our tertiary hospital for thrombolysis and potentially venous stenting of the IVC.

Treatment

Open surgical decompression was discussed with the neurosurgeon but was not indicated because of the partial manifestation of CES and deemed also too high risk with the concomitant use of anticoagulation. The medical team decided to treat the patient with an endovenous approach. As per protocol both popliteal veins were punctured for venous access with placement of two 10 French sheaths. The popliteal, femoral, and common femoral veins were open on venogram. Large amounts of blood clots were removed by thrombosuction from the IVC and both iliac veins with improved venous blood flow. Thrombolysis using alteplase was administered in a split dose through two multisidehole catheters (0.5 mg per hour per catheter) with a split dose of heparin per sheath (5000 IU per 24 hours per sheath). Venous stenting was obviously indicated because of an IVC-stenosis on CTa, however, as the patient was not prepared to undergo sedation and there was no anesthesiologist available, stenting was postponed until the next day.

Clinical symptoms remained similar the next morning. Patency of the femoral and iliac veins was improved on a control-venogram, but the mid IVC remained narrowed on venography, shown in [Figure 3](#), which was also visible with on intravascular ultrasound (IVUS). The anesthesiologist was consulted for peri-procedural sedation. The mid-caval stenosis was stented with a 24 mm x 60 mm sinus-XL stent and extended cranially with a second 24 mm x 60 mm sinus-XL stent, pre- and post-dilated with a 24 mm transluminal angioplasty balloon. Flow substantially improved afterwards. Because of cardiac arrhythmias during the procedure without wire manipulation in the heart, a CTa was performed immediately which excluded pulmonary emboli. The stent was adequately deployed with minimal thrombus proximal to the stent and in the left common iliac vein without limited flow.

Figure 3. Occlusion of the inferior vena cava on venography (left) and stenosis of the inferior vena cava during percutaneous transluminal angiography and venous stenting (B).



Follow-up

Only saddle sensation slightly improved after thrombectomy (day before venous stenting). All symptoms and signs related to CES completely resolved 1 day after venous stenting. The urinary catheter was removed, and neurological findings normalized. The patient was able to mobilize without pain. Stent patency was confirmed with CTa, shown in [Figure 1](#). The patient was discharged after 4

days without signs or symptoms of CES. He was treated with therapeutic dose low-molecular-weight heparin based on therapeutic anti-Xa levels and was switched to a vitamin-K-antagonist at our outpatient clinic after 2 weeks (INR range 2.0–3.0).

The patient was followed up after 6 weeks, 3 months, 6 months, and 1 year. Venous stents and iliofemoral tracts were checked with CTa and duplex ultrasound and have remained patent so far. Symptoms and signs of CES completely resolved until the last date of follow-up and he had no signs of PTS (Villalta score of 2) at the last visit.¹² He even noticed an improved overall fitness level compared with before the thrombotic event, probably caused by opening up the chronic stenosis of the IVC. At the most recent visit, he was switched to a direct oral anticoagulant (apixaban 5 mg, twice daily) because of very instable INR values. An indefinite duration of anticoagulant therapy was discussed with the patient and agreed upon by shared decision making.

Etiology

The hematologist was consulted to screen for thrombotic risk factors and underlying disease or thrombophilia in this young patient with severe presentation of DVT, mild splenomegaly and coincidental finding of a small abnormality around the pyelum of the right kidney. Underlying hematological malignancies, such as malignant lymphoma, were excluded. Infectious diseases were ruled out by serology for the human immunodeficiency virus and various other acute viral infections. Myeloproliferative neoplasms were excluded by molecular diagnostics (JAK2V617F, JAK2 exon 12, CALR, MPL and BCR-ABL all negative), as well as paroxysmal nocturnal hemoglobinuria by flow cytometry. Thrombophilia testing, including the factor V Leiden and prothrombin G20210A mutation, antiphospholipid antibodies including lupus anticoagulant, were all negative and antithrombin, protein C, and protein S levels were normal. No other underlying cause was found for the extensive DVT besides the mid-caval stenosis.

DISCUSSION

To our knowledge this is the first case of CES caused by epidural vein engorgement due to an extensive ilio caval DVT provoked by a chronic stenosis of the IVC. CES completely resolved after thrombectomy, catheter-directed thrombolysis, and stenting of the stenosis in the IVC.

The exact etiology of IVC obstruction is not completely understood. Thrombotic events during early childhood, resulting from pediatric surgery, trauma, malignancy, or neonatal central lines, seem the most likely cause in general, although true congenital absence has also been described.¹³ Based on the collaterals seen on CTa in our patient, it was clear that the IVC stenosis did not occur recently. None of the factors described above affected our patient, besides two minor surgical procedures during childhood. However, an IVC obstruction that originates at a young age may remain asymptomatic over time.¹⁴

Stasis of venous blood around spinal nerves leading to venous congestion, intraneural edema, and nerve compression seem the underlying mechanism causing CES in IVC thrombosis or obstruction.¹⁵ Our patient recovered within 1 day after endovenous intervention and was discharged after 4 days. The quick and complete resolution of the DVT and the IVC stenosis may have prevented remaining disabilities or severe progression of neurological complaints.

CONCLUSION

It is important to timely recognize DVT as a cause of CES and to consider endovenous treatment in a specialized center. Venous stents could restore venous patency and thereby relieve symptoms and signs of CES, in addition to (long-term) therapeutic dose anticoagulation.

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PART VI

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

Up to a quarter of deep vein thrombosis (DVT) is referred to as iliofemoral DVT, in which thrombus is localized in the iliac and/or common femoral veins with or without involvement of the inferior vena cava.¹ Iliofofemoral DVT is often more symptomatic in the acute phase compared to venous thrombosis distal to the common femoral veins. Iliofofemoral DVT is associated with increased risk of post-thrombotic syndrome (PTS).^{2,3} The European Society for Vascular Surgery (ESVS) guidelines on the management of venous thrombosis (2021) recommend: "In selected patients with symptomatic iliofofemoral DVT, early thrombus removal strategies should be considered" (Class IIa, Level A recommendation).⁴ Beside the opportunity for an acute relief of symptoms and signs, this recommendation is based on the reduced risk for PTS development after early clot removal compared to conservative treatment for iliofofemoral DVT.⁴

PART I – ENDOVENOUS MANAGEMENT OF ACUTE DEEP VEIN THROMBOSIS

Chapter 1 focusses on the endovenous treatment of acute DVT and provides a general overview of the challenges, opportunities, and future perspectives of acute iliofofemoral DVT.⁵ Optimal DVT treatment is key in preventing PTS and starts with an appropriate identification of iliofofemoral DVT by visualizing the upper thrombus part. If iliofofemoral DVT is present, referral to expert centers should be considered to discuss treatment options, including early clot removal. This requires an increased awareness of endovenous treatment opportunities and the potential benefits, including an acute relief of symptoms and signs, and reduction of PTS development over time.⁴ A retrospective single-center study identified n= 225 DVTs over a 3-year period, with n= 96 radiographically confirmed as iliofofemoral DVT.⁶ The minority of these patients were referred (n= 3 received thrombolysis). A multidisciplinary approach and intensive collaboration between hospitals possibly helps to improve referral pathways, increase awareness, and optimize treatment of iliofofemoral DVT.

Another hurdle to overcome is the development of an objective, reliable and user-friendly scoring tool to define and grade PTS.⁵ The currently used Villalta score includes both PTS symptoms and clinical signs⁷, which seems insufficient since exercise intolerance and venous claudication are not included. Increased attention to the long-term follow-up of PTS patients is also required to prevent an underestimation, since PTS-related complaints take time to develop after the initial DVT. Lifestyle interventions, such as individualized training programs, may receive a more prominent role in future DVT and PTS management, aiming to improve symptoms and signs and enhance quality of life (QoL).⁸

The use of endovenous treatment followed by venous stent implantation has been increased over the past decades, and appears to be safe for acute ilio-femoral DVT, as well as for PTS.^{9,10} The evolution of (lytic-free) devices, with a decreased risk for bleeding complications, potentially lowers the threshold for considering endovenous treatment of iliofemoral DVT.⁵

PART II – ANTICOAGULANT MANAGEMENT AND RECURRENT VENOUS THROMBOEMBOLISM

Chapter 2 (Bakas et al. Eur J Vasc Endovasc Surg. 2026 Jan 29:S1078-5884(26)00078-X. Epub ahead of print.) describes post-intervention anticoagulant management, recurrent venous thromboembolism, and associations with thrombophilia and left iliac vein compression syndrome after treatment with venous stents for acute DVT and PTS. The cohort involves patients stented between May 2006 and November 2021. Seventy-nine patients were included: 41 DVT and 38 PTS patients. Anticoagulation was continued for 57 (72%) and stopped for 22 (28%) patients. Recurrent VTE occurred in 38% patients (32% DVT; 45% PTS), after median duration of 11 weeks (Q1, Q3: 3, 129): most often in stent re-thrombosis (93%). Primary patency was 62% (n= 49), and secondary patency 94% (n= 74). Most recurrent VTEs (87%) occurred during anticoagulant therapy. Anticoagulation was restarted in all five patients with recurrent VTE after cessation of anticoagulant therapy. Anticoagulant therapy remained stopped in the absence of recurrent VTE (n= 17). Although approximately a quarter of patients experienced VTE after cessation of anticoagulation, stent patency was restored in all cases. Thrombophilia and left iliac vein compression syndrome were not significantly associated with recurrent venous thromboembolism after multivariate analysis ($p>.05$). The findings suggest that cessation of anticoagulant therapy might be considered in selected patients after successful treatment with venous stents. The study serves as a step up to optimization of anticoagulant therapy after treatment with venous stents.

PART III – LONG-TERM RESULTS AFTER VENOUS STENTING FOR ACUTE DEEP VEIN THROMBOSIS AND POST-THROMBOTIC SYNDROME

Patency rates are good after treatment with deep venous stents for DVT and PTS, however less is known about the long-term patency.^{11, 12} **Chapter 3** focusses on long-term patency rates after treatment with deep venous stents for acute DVT and PTS^{13, 14} A total of 53 limbs were stented for acute DVT (median follow-up 2.3 years (IQR: 2.3)) and 76 limbs for PTS (median follow-up 5.2 years (IQR: 7.1)). Re-interventions were typically required within the first year following treatment with venous stents (82.9% of the re-interventions performed within the first year): with primary patency and secondary patency of 73.5% and 98.1%

for acute DVT, and 63.2% and 92.1% for PTS. *'The beginning is the most important part of the work'* – Plato; also in terms of venous stents patency.

Re-interventions were classified according to previously developed scoring systems, including three main categories for re-interventions after venous stenting: technical, flow-related, and/or hematologic.¹⁵ Missed inflow, insufficient flow, and re-thrombosis despite anticoagulation were major causes for re-intervention in our study population.¹³ A substantial part of re-interventions might be preventable by improving our understanding on how to correctly score impaired inflow, and how to identify the perfect landing zone of the stent. The low incidence of permanent occlusion after one year of primary patency suggest that it might be considered to discharge patients from long-term surveillance if no re-intervention occur within the first year, with good inflow at the end of the primary procedure, and continued anticoagulant therapy.

Chapter 4 reported quality of life (using CIVIQ-20 and SF-36 questionnaire) in a cross-sectional cohort of acute DVT and PTS patients after endovenous treatment.^{16,17} The findings highlight that clinicians should be aware of physical disabilities in PTS patients (even when stent remain patent), and to be aware of mental disabilities in terms of QoL after early clot removal for acute DVT.

For acute DVT, 39 patients were included (response rate 73.5%), with a median time of questionnaire completion of 1.8 years (IQR: 3.1) after early clot removal.¹⁶ Median CIVIQ-20 was 29.0 (IQR: 28.0), slightly higher than the minimum of 20.0 ($p < .001$). The median mental and physical component summary did not differ from the normative of 50.0, however a subgroup experienced physical and/or mental disabilities as indicated by the wide interquartile ranges. Common complaints were fatigue and impaired rating of the patients' own health. Re-intervention was associated with a negative (thus worse) impact on the SF-36 mental component summary scale (standardised β coefficient of -0.4 , $p = .030$). Evidence to associate timing of questionnaire completion and QoL was lacking in the study, therefore, the procedure either does not affect mental health, or impaired mental health persists, even after several years. The study findings emphasize the attention mental functioning levels should deserve, beside the widely recognized physical consequences of acute deep vein thrombosis, especially in when re-intervention is required after early clot removal.

For PTS, 45 patients were included (response rate 70.3%), with a median time of questionnaire completion of 6.6 years (IQR: 8.0) after endovenous treatment.¹⁷ For patients with patent stents ($n = 42$), median CIVIQ-20 was 35.5 (IQR: 17.3), higher than the minimum of 20.0 ($p < .001$). Median SF-36 physical component

summary of 44.7 (IQR: 14.2) was significantly lower, and mental component summary of 55.9 (IQR: 7.1), higher than the normative of 50.0 ($p < .001$). The effect of inflow disease (impaired flow of the deep femoral vein and/or femoral vein) was analyzed as well, and was not associated with QoL, however, poor functioning levels were reported for $n = 3$ patients with permanent stent occlusion.

Previous studies have reported improved SF-36 physical component summary scores after treatment with venous stents for PTS, which outcomes further improved after 2 years of follow-up.^{18,19} A significant association between time of questionnaire completion and SF-36 component summaries were lacking in chapter four of the current thesis, suggesting that patients possibly reach a stable phase with consistent functioning levels over time.¹⁷ However, results were evaluated across patients instead of within the same individuals at different time intervals, and should therefore be cautiously interpret. While future studies are required to optimize patient selection regarding who benefit the most of venous stents, the current study revealed that physical disabilities are common at different time points after stenting for PTS. The findings highlight that functioning levels are impaired after stenting for PTS (even if stents remain patent), emphasizing the incurability of this condition. Monitoring PTS complaints during follow-up should be recommended, to consider adjunctive treatment (e.g. lifestyle interventions, compression stockings). Since compromised inflow did not seem to impair QoL in patients with patent stents, we suggest that venous stenting may still be considered in these patients (under the condition that permanent occlusion should be avoided).

PART IV – INFLOW DISEASE IN POST-THROMBOTIC SYNDROME

Chapter 5 demonstrates the importance of adequate pre-procedural inflow in PTS.²⁰ Presence of post-thrombotic lesions in the deep femoral vein and femoral vein were evaluated based on available imaging by three authors. Eighty limbs were included and assigned as having no (37 limbs; 46%), single-vessel (26 limbs; 33%), or double-vessel inflow disease (17 limbs; 21%). One-year primary patency was higher for limbs without inflow disease (89.2%), compared with single-vessel inflow disease (57.7%; $p = .002$), and double vessel inflow disease (47.1%, $p < .001$). No significant differences were found for secondary patency. Inflow disease of the femoral vein was associated with primary patency loss in a multivariate analysis (OR: 10.99; 95%CI: 2.59-46.74; $p = .001$). This chapter emphasizes the strong association of inflow disease with venous stent patency loss, however, the secondary patency remained high. We therefore suggest that the increased risk for re-intervention should be discussed prior to venous stenting to improve decision-making and patient expectations.

It is important to note that assessment of inflow disease was of subjective nature, due to a lack of objective criteria to measure inflow. The reliability of inflow assessment was improved by negotiated consensus after inflow was scored by three authors. The anatomical location of chronic venous obstruction of the iliofemoral tract was scored in another cohort, which demonstrated a strong correlation between classification type and venous stent patency.²¹ Future deep venous research projects should reveal methods to adequately measure inflow, standards to assess “sufficient” inflow, and techniques to improve inflow.

PART V – EXTRAORDINARY CASES OF DEEP VENOUS DISEASE

Chapter 6 provided a systematic literature review of spontaneous iliac vein ruptures.²² A total of 76 cases (64 studies) were evaluated after a systematic literature search. This rare, but frequently lethal condition often affects middle-aged and elderly women (mean age 61 years, 84.2% female), who present with symptoms and signs of a concomitant left-sided DVT while presenting with a retroperitoneal hematoma (96.1% left-sided presentation of spontaneous iliac vein rupture). Spontaneous iliac vein rupture is an easily missed diagnose, even when imaging is performed. A timely identification of the venous rupture brings the opportunity to consider endovascular treatment. Undiagnosed patients frequently underwent open surgery, whereas endovascular or hybrid procedure were common when the diagnose was confirmed. The etiology of spontaneous iliac vein rupture is incompletely understood. There are various hypotheses described for its etiology: mechanical (rupture related to increased pressure due to left-iliac vein compression syndrome), inflammatory (concomitant DVT causes vessel inflammation leading to rupture), and hormonal (common presentation in females aged around 60).²³

Lastly, three cases of spontaneous retroperitoneal hematoma were described in chapter 6, with the clinical presentation of: a spontaneous bleeding around the right iliopsoas muscle due to antiplatelet medication, a spontaneous arterial bleeding around the right kidney subsequently associated with a pheochromocytoma, and a patients with spontaneous iliac vein rupture of the left iliac vein with a concomitant DVT.²⁴

Chapter 7 described a patient with exercise intolerance after acute DVT, which presumably was provoked by inferior vena cava obstruction.²⁵ The patient reported a great improvement after treatment with deep venous stents, including a resolution of symptoms and signs, and improved SF-36 scores comparable to an age-matched Dutch cohort. However, the exact etiology behind the clinical

improvement remains poorly understood. Exercise intolerance was again emphasized as an often underestimated consequence of (ilio)caval obstruction.²⁶

Chapter 8 described a rare case of 30-year-old male patient presenting with a partial cauda equina syndrome, caused by nerve root compression due to venous congestion from an extensive ilio caval acute DVT.²⁷ Complaints of both cauda equina syndrome and acute DVT were completely resolved after endovenous intervention followed by treatment with venous stents. Timely recognition of acute DVT as a cause of cauda equina syndrome is important for considering endovenous treatment options in a specialized center. Venous stents could restore venous patency, and thereby relieve concomitant symptoms and signs of cauda equina syndrome, in addition to (long-term) therapeutic dose anticoagulation.

FUTURE PERSPECTIVES

“Prevention (of post-thrombotic syndrome) is better than cure”

Post-thrombotic syndrome is incurable, the treatment is focussed on symptom relief. The incurability of PTS was again emphasized in chapter four, with lowered functioning levels in a cross-sectional PTS population with patent venous stents.¹⁷ Improved awareness of acute iliofemoral DVT and the frequently devastating consequences at the long-term (post-thrombotic syndrome), should help to early identify candidates for endovenous treatment and offer them a clot-free future. Optimized management of DVT in the acute phase is important to prevent PTS in the chronic phase. It requires a multidisciplinary approach and intensive collaboration between treating hospitals to improve referral pathways for endovenous treatment of acute iliofemoral DVT.⁶

Quality of life in PTS: “Physical functioning should be monitored in post-thrombotic syndrome, even after successful treatment with venous stent”

Clinicians should be aware of physical disabilities in PTS patients, even after successful treatment with venous stents.¹⁷ Monitoring patient complaints, functioning levels, and QoL during follow-up brings the opportunity to consider adjunctive treatment (e.g., compression therapy and lifestyle interventions). Future QoL studies should investigate the efficacy and feasibility of out of hospital monitoring for detecting patients with moderate to severe symptoms and signs of PTS. For example, patient-reported Villalta scales (with visually assisted forms) is an acceptable tool for diagnosing and grading PTS.²⁸ Also the development and use of e-health consultation and additional mobile applications in the DVT and PTS population require further investigation. Future studies should aim to predict QoL based on covariates prior to endovenous treatment. An accurate prediction of QoL may help to identify whether treatment with venous stents is expected to be beneficial in terms of expected QoL after treatment with venous stents.

Quality of life in acute DVT: “Mental functioning deserves attention after invasive treatment for acute deep vein thrombosis”

Beside the widely recognized physical consequences of iliofemoral DVT, mental functioning levels deserve a particular attention in patients stented for acute DVT.¹⁶ Methods to support mental functioning levels in acute DVT, especially after early clot removal, should be revealed. Clinicians should be aware of the potential mental consequences of acute iliofemoral DVT and early clot removal, especially if re-intervention is required.

Cessation of anticoagulant therapy: “As simple as possible, but not simpler”

Strict protocols for cessation of post-interventional anticoagulant therapy after DVT and PTS treatment with venous stents are currently lacking. The safety and feasibility of protocols for cessation of anticoagulant therapy should be further investigated to optimize post-intervention anticoagulant management. These studies should also help to clearly define whether left iliac vein compression syndrome qualifies as a provoking factor for DVT. Patients with left iliac vein compression syndrome may receive indefinite anticoagulation therapy, however, if left iliac vein compression syndrome qualifies as a provoking factor for DVT cessation of anticoagulant therapy might be safe when venous compression is successfully resolved by venous stents.

Inflow: “If you cannot measure inflow, you cannot improve it”

Mounting evidence has suggested the crucial role that pre-operative inflow plays in terms of venous stent patency in PTS.^{15,20,21} While the importance of inflow disease has been emphasized, objective criteria to quantify “sufficient inflow” are still missing. The optimal diagnostic method to adequately measure inflow should still be revealed in order to subsequently define cut-off values for inflow disease with expected risks for patency loss. Beside improving the pre-operative assessment of inflow disease, future research should investigate techniques to treat inflow, for example balloon angioplasty to treat compromised inflow adjunctive to treatment with venous stents.²⁹, improved mechanical thrombectomy devices to treat chronic venous lesions.³⁰, or other innovations such as improved (possibly drug-eluting, or soluble) venous stents.

Extraordinary cases: “A stent for every task”

Endovenous treatment with deep venous stents has been involved in various extraordinary cases. Chapter six has outlined spontaneous iliac vein ruptures, chapter seven described exercise intolerance caused by vena cava atresia, and a rare case of cauda equina syndrome caused by extensive iliocaval thrombosis was outlined in chapter eight. The applicability of venous stents in various extraordinary cases, show the great applicability this type of treatment has. To some extent, there will possibly be a stent for every task.

ALGEMENE DISCUSSIE

Bij ongeveer een kwart van de diep veneuze tromboses (DVT) breidt het stelsel uit naar de iliacaal venen en/of vena femoralis communis en eventueel de vena cava inferior: bekend als een iliofemorale DVT.¹ Bij een iliofemorale DVT zijn de symptomen vaak heviger in de acute fase dan bij een trombose van de venen distaal van de vena femoralis communis gelegen. Daarnaast brengt een iliofemorale DVT een verhoogd risico op het posttrombotisch syndroom (PTS) met zich mee.^{2,3} De European Society for Vascular Surgery (ESVS) richtlijn ten aanzien van de behandeling van veneuze trombose (2021) adviseert een interventie te overwegen (early clot removal) bij een geselecteerde groep patiënten met symptomatische iliofemorale DVT (Class IIa, Level A recommendation; *"In selected patients with symptomatic iliofemoral DVT, early thrombus removal strategies should be considered"*).⁴ Naast de mogelijkheid om acute klachten en symptomen te verlichten, is deze aanbeveling gebaseerd op het gereduceerde risico op het ontwikkelen van PTS na een interventie voor acute iliofemorale DVT vergeleken met een conservatieve behandeling.

DEEL I – ENDOVENEUZE BEHANDELING VAN ACUTE DIEP VENEUZE TROMBOSE

Hoofdstuk 1 richt zich op endoveneuze behandeling voor acute DVT in het algemeen, en geeft een overzicht van de uitdagingen, mogelijkheden en toekomstige perspectieven bij iliofemorale DVT.⁵ Een optimale behandeling van acute DVT is de hoeksteen ten aanzien van de preventie van PTS. Dit begint bij het adequaat identificeren van acute iliofemorale DVT door in kaart te hebben in welk vat het craniale deel van de DVT zich bevindt. Indien er sprake is van een acute iliofemorale DVT, zou een verwijzing naar een expertise centrum overwogen moeten worden, voor een zorgvuldig besluit tot (eventueel endoveneuze) behandeling. Om deze overwegingen aan te moedigen, is bewustzijn van de endoveneuze behandelopties en potentiële voordelen hiervan noodzakelijk: zoals een directe verlichting van klachten en symptomen in de acute fase en potentieel lager risico op PTS in de periode hierna.⁴ Een retrospectieve single-center studie identificeerde $n = 225$ DVTs over een periode van 3 jaar, waarbij in $n = 96$ casus een iliofemorale DVT radiologisch bevestigd werd.⁶ De minderheid van deze patiënten ($n = 3$) werd doorverwezen ($n = 3$ ondergingen interventie middels trombolyse). Een multidisciplinaire aanpak en intensieve samenwerking tussen ziekenhuizen helpt mogelijk het bewustzijn van acute iliofemorale DVT en de te overwegen behandelopties te verbeteren, de behandeling te optimaliseren en om toekomstige doorverwijzingen gemakkelijker te laten verlopen.

Een andere uitdaging is de ontwikkeling van een objectief, betrouwbaar en gebruiksvriendelijk scoremodel voor het definiëren en classificeren van PTS.⁵ Momenteel is de Villalta score een gangbare manier om symptomen en klinische tekenen van PTS te diagnosticeren⁷, echter klachten zoals verminderde inspanningstolerantie en veneuze claudicatie komen niet aan bod in dit scoresysteem. Aandacht voor de lange termijn follow-up van PTS is eveneens van belang, aangezien het tijd in beslag neemt om PTS-gerelateerde klachten te ontwikkelen na de initiële DVT. Leefstijl interventies, zoals geïndividualiseerde trainingsprogramma's, kunnen mogelijk een belangrijke rol spelen rondom DVT en PTS met als doel symptomen, klachten en kwaliteit van leven te verbeteren.⁸

De toepassing van endoveneuze behandelopties gevolgd door veneuze stent-plaatsing is toegenomen over de afgelopen decennia, en blijkt een veilige techniek voor acute DVT, zo ook voor de behandeling van PTS.^{9,10} De ontwikkeling van nieuwe apparatuur, met een verlaagd risico op bloedingen, maakt mogelijk de overweging van endoveneuze behandelopties laagdrempeliger bij iliofemorale DVT.⁵

DEEL II – ANTISTOLLING EN RECIDIVERENDE VENEUZE THROMBO-EMBOLIE

Hoofdstuk 2 (Bakas et al. Eur J Vasc Endovasc Surg. 2026 Jan 29:S1078-5884(26)00078-X. Epub ahead of print.) beschrijft post-interventionele antistolling, recidiverende veneuze trombo-embolie, en associaties met trombofilie en left iliac vein compression syndrome na behandeling met veneuze stents voor DVT en PTS. Het cohort betreft patiënten die een veneuze stentplaatsing ondergingen tussen mei 2006 en november 2021. Er werden 79 patiënten geïnccludeerd: n= 41 DVT en n= 38 PTS. Antistolling werd gecontinueerd bij 57 (72%) en gestaakt bij 22 (28%) patiënten. Bij 38% van de patiënten (32% DVT; 45% PTS), was sprake van een recidief VTE na een mediane duur van 11 weken (Q1, Q3: 3, 129): meestal in stent re-trombose (93%). Primaire doorgankelijkheid was 62% (n= 49) en secundair 94% (n= 74). De meeste VTEs (87%) ontstonden tijdens gebruik van antistolling. Antistolling werd herstart in alle vijf patiënten met recidief VTE na het staken van antistolling. Antistolling bleef gestaakt indien geen recidief VTE optrad (n= 17). Hoewel bij ongeveer een kwart van de patiënten een VTE optrad na het staken van antistolling, werd doorgankelijkheid van stents hersteld in alle casus. Trombofilie en left iliac vein compression syndrome waren niet significant geassocieerd met recidief VTE na multivariate analyse (p>.05). De bevindingen uit dit hoofdstuk suggereren dat het staken van antistolling overwogen kan worden in geselecteerde patiënten na een geslaagde behandeling met veneuze stents. Toekomstige studies moeten helpen

deze groep nader te definiëren en daarmee post-interventionele antistolling na veneuze stentplaatsing voor DVT en PTS te optimaliseren.

DEEL III – LANGE TERMIJN RESULTATEN NA VENEUZE STENTPLAATSING VOOR ACUTE DIEP VENEUZE TROMBOSE EN POSTTROMBOTISCH SYNDROOM

Uitkomsten ten aanzien van de doorgankelijkheid van diep veneuze stents voor DVT en PTS zijn veelbelovend, hoewel minder bekend is over de lange termijn uitkomsten.^{11, 12} **Hoofdstuk 3** laat zien dat de doorgankelijkheid van veneuze stents op de lange termijn hoog is bij patiënten met acute DVT en PTS.^{13, 14} In totaal werden 53 benen gestent voor acute DVT (mediane follow-up van 2.3 jaar (IQR: 2.3)) en 76 benen voor PTS (mediane follow-up van 5.2 jaar (IQR: 7.1)). Re-interventies vonden hoofdzakelijk plaats binnen het eerste jaar van follow-up na veneuze stentplaatsing (82.9% van de re-interventies in het eerste jaar): met een primaire doorgankelijkheid en secundaire doorgankelijkheid van 73.5% en 98.1% voor acute DVT, en 63.2% en 92.1% voor PTS. *‘The beginning is the most important part of the work’* – Plato; zo ook geldt dit voor de doorgankelijkheid van veneuze stents.

Re-interventies werden ingedeeld op basis van een scoremodel, waarbij drie hoofd categorieën voor oorzaken van re-interventies werden gehanteerd: technisch, flow-gerelateerd en/of hematologisch.¹⁵ Ontbreken van inflow, insufficiënte flow, en re-trombose (ondanks adequate antistolling) waren veelvoorkomende oorzaken voor re-interventie in onze studie.¹³ Een substantieel deel van de re-interventies is mogelijk te voorkomen door een beter begrip van inflow, waaronder wanneer inflow dusdanig aangedaan is dat de flow beperkingen klinisch relevant zijn; en door het optimaliseren van ideale landingszone van de stent. De lage incidentie van permanente stent occlusie na een primaire doorgankelijkheid in het eerste jaar, suggereert dat poliklinische follow-up niet meer strikt noodzakelijk is op de lange termijn zolang er geen re-interventie heeft plaatsgevonden in het eerste jaar, de inflow voldoende is, en patiënten antistolling continueren.

Hoofdstuk 4 bracht kwaliteit van leven (middels CIVIQ-20 en SF-36 vragenlijsten) in kaart in een cross-sectioneel cohort van patiënten endoveneus behandeld voor acute DVT en PTS.^{16,17} Aandacht voor fysiek functioneren bij PTS, ook na succesvolle veneuze stentplaatsing met patente stents gedurende follow-up werd behandeld in dit hoofdstuk. Zo ook kwamen de aspect van mentaal functioneren bij acute DVT na endoveneuze behandeling aan bod.

Voor acute DVT werden 39 patiënten geïnccludeerd (response rate 73.5%), met een mediane tijd van 1.8 jaar (IQR: 3.1) tussen het invullen van de vragenlijst en endoveneuze behandeling.¹⁶ Mediane CIVIQ-20 was 29.0 (IQR: 28.0), en minimaal hoger dan de minimum CIVIQ-20 waarde van 20.0 ($p < .001$). De mediane mentale en fysieke component toonden geen verschil ten opzichte van de norm van 50.0, hoewel de wijde interkwartiele afstanden suggestief zijn voor fysieke en/of mentale beperkingen in een subgroep. Frequent voorkomende klachten waren vermoeidheid en een lagere inschatting van de gesteldheid van de eigen gezondheid. Re-interventie werd geassocieerd met negatieve (oftewel slechtere) impact op de SF-36 mentale component (standardised β coefficient van -0.4 , $p = .030$). De tijd na het invullen van de vragenlijsten kon echter niet geassocieerd worden met kwaliteit van leven in de studie: mogelijk heeft de procedure geen invloed op mentale gesteldheid, of mentale beperkingen blijven consistent (ook meerdere jaren tijd na endoveneuze behandeling). De studie benadrukt dat belangstelling voor mentaal functioneren belangrijk is, naast de bekende fysieke consequenties van acute DVT, in het bijzonder indien een re-interventie noodzakelijk is na endoveneuze behandeling.

Voor PTS, werden 45 patiënten geïnccludeerd (response rate 70.3%), met een mediane tijd van 6.6 jaar (IQR: 8.0) tussen het invullen van de vragenlijst en endoveneuze behandeling.¹⁷ Voor patiënten met doorgankelijke stents ($n = 42$), was de mediane CIVIQ-20 35.5 (IQR: 17.3), hoger dan de minimum waarde van 20.0 ($p < .001$). De mediane SF-36 fysieke component van 44.7 (IQR: 14.2) was significant lager, en de mentale component van 55.9 (IQR: 7.1), hoger dan de norm van 50.0 ($p < .001$). Het effect van inflow beperkingen (aangedane flow van de vena femoralis en/of vena femoralis profunda) werd eveneens geanalyseerd, maar bleek niet significant geassocieerd te zijn met kwaliteit van leven. Echter, slechte functionele uitkomsten werden gerapporteerd voor $n = 3$ patiënten met permanente stent occlusie.

Voorgaande studies lieten verbeterde uitkomsten van de SF-36 fysieke component zien na behandeling van PTS met veneuze stents, waarvan de uitkomsten verder verbeterden na 2 jaar follow-up.^{18,19} In hoofdstuk vier van dit proefschrift werd geen significante associatie aangetoond tussen de tijd van het invullen van de vragenlijst en SF-36 uitkomsten, suggestief voor een mogelijk stabiele fase waarbij patiënten consistente functionele uitkomsten vertonen in verloop van tijd.¹⁷ Echter, is een voorzichtige interpretatie van de data noodzakelijk. Zo werden de resultaten geëvalueerd tussen patiënten na behandeling in plaats van tussen dezelfde patiënten op verschillende tijdstippen. Hoewel toekomstige studies nodig zijn voor een verbeterde patiëntselectie voor behandeling met veneuze stents, laat het huidige onderzoek zien dat fysieke beperkingen frequent

zijn op verschillende tijdstippen na stentplaatsing voor PTS. Dat functionele uitkomsten beperkt zijn na stentplaatsing voor PTS (ook als de doorgankelijkheid van de stents behouden blijft), benadrukt dat PTS een ongeneeslijke aandoening is. Het monitoren van PTS klachten gedurende follow-up is van belang om eventuele aanvullende behandelingen te overwegen (zoals leefstijlinterventies, compressiekousen). Dat aangedane inflow niet geassocieerd werd met kwaliteit van leven in patiënten met doorgankelijke stents, suggereert dat veneuze stentplaatsing ook binnen deze groep PTS patiënten overwogen kan worden (onder voorwaarde dat een permanente occlusie voorkomen wordt).

DEEL IV – AANGEDANE INFLOW BIJ POSTTROMBOTISCH SYNDROOM

Hoofdstuk 5 toont het belang van “inflow” in PTS patiënten die een behandeling met veneuze stents ondergaan.²⁰ De aanwezigheid van posttrombotische laesies in de vena femoralis en vena femoralis profunda werd geevalueerd op basis van beschikbare beeldvorming door drie auteurs. Tachtig benen werden geïnccludeerd en ingedeeld als geen inflow beperking (37 benen; 46%), één-vat inflow beperking (26 benen; 33%), of twee-vat inflow beperking (17 benen; 21%). De 1-jaar primaire doorgankelijkheid was hoger voor benen zonder inflow beperking (89.2%), vergeleken met één-vat inflow beperking (57.7%; $p=.002$), en twee-vat inflow beperking (47.1%, $p<.001$). Geen significante verschillen werden gevonden voor secundaire doorgankelijkheid. Inflow beperkingen van de vena femoralis werd geassocieerd met verlies van de primaire doorgankelijkheid van veneuze stents in een multivariate analyse (OR: 10.99; 95%CI 2.59-46.74; $p=.001$). Dit hoofdstuk benadrukt de sterke associatie van inflow beperkingen met verlies van veneuze stent patency, hoewel de secundaire patency hoog is. Naar aanleiding van deze bevindingen is het van belang het verhoogde risico op re-interventie te bespreken vooraf aan eventuele behandeling met veneuze stents, wat mogelijk de besluitvorming en patiëntverwachtingen kan verbeteren.

Een belangrijk punt om te benoemen is het gegeven dat het evalueren van inflow beperkingen van subjectieve aard was, aangezien objectieve criteria om inflow te evalueren momenteel ontbreken. De betrouwbaarheid van de inschatting van inflow werd verhoogd middels “negotiated consensus” na het scoren van inflow door drie auteurs. De anatomische locatie van chronische veneuze obstructie in het iliofemoraal traject werd gescoord in een ander cohort, waarbij een sterke correlatie gevonden werd tussen classificatie type en veneuze stent patency.²¹ Toekomstig onderzoek op diep veneus gebied moet aantonen welke methode gebruikt dient te worden om inflow adequaat te scoren, welke stan-

daard gebruikt moet worden om inflow als voldoende te beschouwen, en welke technieken overwogen kunnen worden om inflow te verbeteren.

DEEL V – UITZONDERLIJKE DIEP VENEUZE CASUÏSTIEK

In **hoofdstuk 6** werd een systematisch literatuuronderzoek uitgevoerd naar spontane vena iliacerupturen.²² In totaal werden 76 casus (64 studies) geëvalueerd na een systematische zoekopdracht van de literatuur. Een dergelijke ruptuur is zeldzaam, echter in veel gevallen levensbedreigend. Het betreft in de meeste gevallen vrouwen van oudere of middelbare leeftijd (gemiddelde leeftijd 61 jaar, 84.2% vrouw), die zich presenteren met een linkszijdige trombosebeen tijdens hun presentatie met een retroperitoneaal hematoom (96.1% linkszijdige presentatie). Spontane vena iliaca rupturen worden gemakkelijk gemist, ondanks aanvullende beeldvorming. Een tijdige diagnose is echter van belang voor het overwegen van een endovasculaire behandeling. Bij het ontbreken van de diagnose ondergaan patiënten frequenter open chirurgische interventie, terwijl endovasculaire of hybride procedures vaak verricht worden als de diagnose bevestigd is. De etiologie van spontane vena iliacerupturen is nog niet geheel duidelijk. Er zijn verschillende hypothesen voor de ontstaanswijze: mechanische (ruptuur gerelateerd aan een verhoogde druk door left-iliac vein compression syndroom), inflammatoir (gelijktijdige DVT veroorzaakt inflammatie van het vat, waardoor een verhoogd ruptuurrisico optreedt), en hormonaal (vanwege de frequente presentatie in vrouwen van middelbare leeftijd).²³

De klinische presentatie van drie casus met een spontaan retroperitoneaal hematoom werd eveneens beschreven in hoofdstuk 6: een spontane bloeding rond de rechter musculus iliopsoas als gevolg van antistolling, een spontane arteriële bloeding rond de rechter nier geassocieerd met een feochromocytoom en een patiënt met linkszijdige spontane vena iliaca ruptuur met een gelijktijdige DVT.²⁴

In **hoofdstuk 7** werd een patiënt met inspanningsintolerantie als gevolg van obstructieve veranderingen van de vena cava inferior beschreven.²⁵ De patiënt bemerkte een verbetering na behandeling met diep veneuze stents, waaronder vermindering van klachten en symptomen en verbeterde SF-36 scores vergeleken met een Nederlands cohort van vergelijkbare leeftijd. De exacte etiologie waardoor de klinische verbetering na stentplaatsing verklaard kan worden blijft echter onvoldoende begrepen. De studie benadrukt dat inspanningsintolerantie een onderschatte consequentie kan zijn van (ilio)cavale obstructie.²⁶

In **hoofdstuk 8** wordt een case-report beschreven over een 30-jarige man met een partiële cauda equina syndroom door zenuwwortelcompressie als gevolg van veneuze stuwings bij uitgebreide acute ilio-cavale DVT.²⁷ De patiënt werd

succesvol behandeld middels trombolyse gevolgd door veneuze stentplaatsing en langdurige therapeutische antistolling, waarna klachten en symptomen van cauda equina syndroom en acute DVT verholpen werden. Het is van belang een acute diep veneuze trombose tijdig te herkennen als (zeldzame) oorzaak van het cauda equina syndroom, zodat een endoveneuze behandeling in een gespecialiseerd centrum kan worden overwogen. Veneuze stents kunnen veneuze doorankelijkheid herstellen, waardoor (zeldzaam optredende) gelijktijdige klachten van cauda equina syndroom verholpen worden, met aanvullend therapeutische antistolling op de lange termijn.

TOEKOMSTPERSPECTIEVEN

“Voorkomen (van posttrombotisch syndroom) is beter dan genezen”

Posttrombotisch syndroom is niet te genezen, de behandeling richt zich op de bestrijding van symptomen. Dat PTS ongeneeslijk is, werd nogmaals benadrukt in hoofdstuk 4, waar lagere functionele uitkomsten geobjectiveerd werden in een cross-sectioneel cohort van PTS patiënten met doorgankelijke veneuze stents. Toegenomen kennis van acute iliofemorale DVT en de potentieel ernstige gevolgen op de lange termijn (PTS), draagt mogelijk bij aan een tijdige identificatie van patiënten die in aanmerking komen voor een endoveneuze behandeling en kan hen een stolselvrije toekomst geboden worden. Geoptimaliseerde behandeling van DVT in de acute fase is immers van belang om PTS te voorkomen in de chronische fase. Een multidisciplinaire aanpak en intensieve samenwerking tussen behandelende ziekenhuis is van belang om de doorverwijzing voor endoveneuze behandeling van acute iliofemorale DVT gemakkelijker te laten verlopen.⁶

Kwaliteit van leven in PTS: “Fysiek functioneren zou gemonitord moeten worden in PTS, ook na succesvolle behandeling met veneuze stents”

Het is van belang dat clinici bewust zijn van de fysieke beperkingen die PTS patiënten kunnen ervaren, ook na succesvolle behandeling met veneuze stents.¹⁷ Het monitoren van kwaliteit van leven tijdens poliklinische follow-up en het overwegen van aanvullende behandelingen (zoals elastische compressiekousen en leefstijlinterventies) wordt aanbevolen. Toekomstige studies met betrekking tot kwaliteit van leven, zouden zich moeten richten op het in kaart brengen van de efficiëntie en haalbaarheid van thuismonitoring van patiënten na een acute DVT. Bijvoorbeeld patiënt-gerapporteerde Villalta scores (met ondersteuning van visuele vragenlijsten) bleken een acceptabele manier voor het diagnosticeren en graderen van PTS.²⁸ Ook het ontwikkelen en gebruiken van e-health consultatie en aanvullende mobiele applicaties in DVT en PTS patiënten vergt nader onderzoek. Daarnaast zouden deze studies zich moeten richten op hoe preoperatieve waardes, de postoperatieve kwaliteit van leven kunnen voorspellen. Op die manier kan mogelijk beter in kaart gebracht worden bij wie behandeling met veneuze stents het gewenste resultaat biedt op gebied van kwaliteit van leven.

Kwaliteit van leven in acute DVT: “Mentaal functioneren verdient aandacht na invasieve behandeling voor acute DVT”

Naast de bekende fysieke consequenties van acute iliofemorale DVT, is aandacht voor de mentale aspecten van belang, in het bijzonder na endoveneuze behandeling.¹⁶ De meerwaarde van peri-procedurele mentale ondersteuning bij invasieve behandeling van acute DVT, dient nader onderzocht te worden, in het bijzonder indien re-interventies worden uitgevoerd.

Staken van antistolling: “Zo eenvoudig mogelijk, maar niet eenvoudiger”

Er is een vraag naar gestandaardiseerde richtlijnen voor het staken van post-interventionele antistolling na veneuze stentplaatsing voor acute DVT en PTS. De veiligheid en haalbaarheid van het staken van post-interventionele antistolling dient nader onderzocht te worden. Toekomstige studies moeten eveneens onthullen of left iliac vein compression syndrome gezien mag worden als uitlokkende factor voor DVT. Patiënten met left iliac vein compression syndrome krijgen momenteel mogelijk voor onbepaalde duur antistolling voorgeschreven, hoewel het wellicht veilig is antistolling te staken indien left iliac vein compression syndrome beschouwt mag worden als uitlokkende factor voor DVT (onder de voorwaarde dat het compressiepunt verholpen is na succesvolle behandeling met veneuze stents).

Inflow beperkingen: “Zolang je inflow niet kan meten, kan je het niet verbeteren”

Bewijs dat pre-operatieve inflow een cruciale rol speelt ten aanzien van de doorgankelijkheid van veneuze stents in PTS neemt toe.^{15,20,21} Hoewel het belang van inflow steeds vaker benadrukt wordt, ontbreken objectieve criteria om dit accuraat te kwantificeren. De optimale diagnostiek om inflow adequaat te meten dient nader onderzocht te worden, zodat afkapwaardes met te verwachten risico's voor re-interventie in kaart gebracht kunnen worden vooraf aan veneuze stentplaatsing. Zo ook dienen technieken om aangedane inflow te behandelen onderzocht te worden. Bijvoorbeeld ballon angioplastiek om aangedane inflow te behandelen in aanvulling op behandeling met veneuze stents.²⁹ Verbeterde mechanische thrombectomie technieken om chronische veneuze laesies te behandelen.³⁰ Of andere innovaties, zoals verbeterde veneuze stents (mogelijk medicamenteus geïmpregneerd, of oplosbaar).

Buitengewone casuïstiek: “Een stent voor ieder doel”

Endoveneuze behandeling met diep veneuze stents is betrokken geweest bij de behandeling van verschillende buitengewone casuïstiek. Hoofdstuk zes omschreef spontane vena iliaca rupturen, hoofdstuk zeven inspanningsintole-

rantie bij vena cava atresia, en een zeldzame casus van cauda equina syndroom veroorzaakt door iliocaval trombose kwam aan bod in hoofdstuk acht. Dit toont de brede toepasbaarheid van dit type behandeling en biedt potentie. Tot op zekere hoogte, is er in de nabije toekomst mogelijk voor iedere taak een stent beschikbaar.

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PART VII

SUMMARY AND APPENDICES

SUMMARY IN ENGLISH

Patients with an iliofemoral or ilio caval deep vein thrombosis (DVT) will develop post-thrombotic syndrome (PTS) more frequently than patients with a femoropopliteal or calf vein DVT. Treatment with venous stents could relieve acute symptoms and signs of DVT and decrease the risk of PTS development. Interventions followed by placement of venous stents are performed to treat symptoms and signs of PTS in the chronic phase as well. Endovenous treatment techniques with venous stents for acute DVT and PTS have been increasingly performed over the past decades. The optimal duration of antithrombotic management after treatment with venous stents, and whether left iliac vein compression syndrome counts as a provoking factor for DVT is unknown. Cessation of post-interventional anticoagulant therapy might be safe for a selected group of patients, but requires confirmation by prospective studies.

Patency loss is common within the first year after treatment with venous stents, but secondary patency is high at the long-term. Primary patency, secondary patency, and permanent occlusion were 73.5%, 98.1%, and 1.9% after treatment with venous stents for acute DVT (n= 53 limbs) after median follow-up of 2.3 years (IQR: 2.3); and 63.2%, 92.1%, and 7.9% for PTS (n= 76 limbs) after median follow-up of 5.2 years (IQR 7.1). Patient-reported outcome measures showed that physical disabilities are common, even after successful treatment with venous stents for PTS, emphasising that prevention of PTS is better than cure. The Short Form Health Survey (SF-36) physical and psychological component summaries were compared with the normative value of 50.0 (general population of the United States), with higher scores indicating better quality of life. Median physical component summary of the SF-36 was 44.7 (IQR: 14.2) after treatment with venous stents for PTS, lower than the normative (50.0), $p < .001$. However, median psychological component summary of the SF-36 was 55.9 after treatment with venous stents for PTS, higher than the normative (50.0), $p = .001$. Impaired inflow of the deep femoral vein and femoral vein did not impact quality of life, but PTS patients with occluded stents (n= 3) reported poor functioning levels. For acute DVT patients, attention to mental functioning levels is deserved besides attention to the physical consequences after treatment. The median physical components summary (median 50.5, IQR: 16.6) and mental component summary (median 50.2, IQR: 14.2) of the SF-36 did not differ from the normative of 50.0 for acute DVT, however, wide interquartile ranges indicated impairments for a subgroup of patients. Re-intervention showed a significantly negative impact on SF-36 mental component summary in acute DVT (standardized β coefficient of -0.4, $p = .030$). We also found that assessment of pre-operative inflow of the deep femoral vein and femoral vein is important, since impaired inflow

increases the risk for stent patency loss in PTS. Eighty limbs with venous stents for PTS were evaluated: 37 limbs (46%) without inflow disease, 26 limbs (33%) with single-vessel inflow disease, and 17 limbs (21%) with double-vessel inflow disease. One-year primary patency was higher for limbs without inflow disease (89.2%), compared with single-vessel (57.7%, $p=.002$), and double-vessel inflow disease (47.1%, $p<.001$). Presence of inflow disease was significantly associated with 1-year primary patency loss (OR: 7.17; [95%CI:2.16 – 23.78], $p=.001$). Future research should develop objective criteria to define “sufficient inflow”, and develop methods to improve inflow as well.

Treatment with venous stents was involved in various extraordinary cases, including spontaneous iliac vein rupture, chronic inferior vena cava obstruction presenting with exercise intolerance, and cauda equina syndrome caused by DVT. Spontaneous iliac vein rupture is a rare and easily missed diagnosed, with 76 cases (64 studies) presented in the literature. The diagnose should especially be considered for middle-aged and elderly female patients who present with haemorrhagic shock and concomitant left-sided DVT. Treatment of spontaneous iliac vein rupture could be either conservative, endovascular, or open-surgical. Patients with chronic inferior vena cava obstruction, may present with exercise intolerance without any leg-specific symptoms or signs. Treatment with venous stents was successfully performed in a case-report, with improved hemodynamic, enhanced exercise intolerance and quality of life. Another case-report demonstrated DVT as a rare cause of cauda equina syndrome, with successful resolution of both conditions after thrombolysis, followed by treatment with venous stents. Timely recognition of DVT as a cause of cauda equina is important, and brings the opportunity to consider endovenous treatment. The extraordinary cases above demonstrate the great applicability and future perspectives of endovenous treatment methods.

SAMENVATTING IN HET NEDERLANDS

Patiënten met een iliofemorale of ilio cavale diepe veneuze trombose (DVT) ontwikkelen vaker posttrombotisch syndroom (PTS) dan patiënten met een femoropopliteale of kuitvene trombose. Behandeling met veneuze stents verlicht acute symptomen en klachten van DVT en verlagen mogelijk het risico op de ontwikkeling van PTS. Interventies gevolgd door het plaatsen van veneuze stents worden ook gebruikt in de chronische fase ter behandeling van PTS. De toepassing van een endoveneuze behandeling met veneuze stents voor acute iliofemorale DVT en PTS is toegenomen over de afgelopen decennia. De optimale antistollingsduur na veneuze stentplaatsing is onduidelijk. Ook is onzeker of "left iliac vein compression syndrome" een uitlokkende factor voor DVT is. Het staken van post-procedurele antistolling lijkt veilig in een geselecteerde groep patiënten, wat nadere bevestiging vereist in prospectief onderzoek.

Verlies van de doorgankelijkheid van de stent treedt frequent op binnen het eerste jaar na de behandeling. De secundaire doorgankelijkheid is echter hoog op de lange termijn. Primaire doorgankelijkheid, secundaire doorgankelijkheid en permanente occlusie waren 73.5%, 98.1%, en 1.9% voor acute DVT (n= 53 benen) na een mediane follow-up van 2.3 jaar (IQR: 2.3); en 63.2%, 92.1%, en 7.9% voor PTS (n= 76 benen) na een mediane follow-up van 5.2 jaar (IQR: 7.1). Patiënt-gereporteerde uitkomstmaten laten zien dat fysieke beperkingen geregeld voor komen bij PTS: ook na succesvolle behandeling met veneuze stents. Kortom het voorkomen van PTS is beter dan genezen. De Short Form Health Survey (SF-36) "physical component summary" (fysiek) en "psychological component summaries" (mentaal) werden vergeleken met de referentiewaarde van 50.0 (algemene populatie van de Verenigde Staten), waarbij hogere scores een betere kwaliteit van leven representeren. De mediane "physical component summary" van de SF-36 was 44.7 (IQR: 14.2) na behandeling van PTS met veneuze stents, significant lager dan de referentiewaarde (50.0), $p < .001$. De mediane "psychological component summary" van de SF-36 was daarentegen 55.9 na behandeling van PTS met veneuze stents: significant lager dan de referentiewaarde (50.0), $p = .001$. Aangedane inflow van de vena femoralis en vena femoralis profunda was niet geassocieerd met een verminderde kwaliteit van leven. Na permanente stent occlusie (n= 3) werden lage functionele uitkomsten gerapporteerd. Na stentplaatsing voor acute DVT, is extra aandacht voor mentale aspecten gerechtvaardigd naast aandacht voor de fysieke consequenties. De "physical component summary" (mediaan 50.5, IQR: 16.6) en "mental component summary" (mediaan 50.2, IQR: 14.2) van de SF-36 lieten geen significante verschillen zien met de referentiewaarde van 50.0 voor acute DVT, echter, suggereren de brede interkwartiele afstanden (IQR) beperkingen voor individuen. Re-interventie werd

significant geassocieerd met lagere “mental component summaries” na behandeling voor acute DVT. Pre-operatieve inflow van de vena femoralis profunda en vena femoralis is van belang, aangezien aangedane inflow de kans op het verlies van doorgankelijkheid van veneuze stents voor PTS verhoogd. Tachtig benen met veneuze stents voor PTS werden geëvalueerd: 37 benen (46%) zonder aangedane inflow, 26 benen (33%) met “één-vat” aangedane inflow, en 17 benen (21%) met “twee-vat” aangedane inflow. Primary patency na 1 jaar was hoger voor patiënten zonder aangedane inflow (89.2%), vergeleken met één-vat (57.7%, $p=.002$), en twee-vat aangedane inflow (47.1%, $p<.001$). Aangedane inflow werd significant geassocieerd met verlies van primary patency binnen het eerste jaar (OR: 7.17; [95%CI:2.16 – 23.78], $p=.001$). Toekomstige studies moeten zich richten op het ontwikkelen van objectieve criteria wanneer inflow “voldoende” is, eveneens op de ontwikkeling van methodes om inflow te verbeteren.

Tot slot, werden veneuze stents toegepast bij verschillende buitengewone casus: inspanning intolerantie bij chronische vena cava inferior obstructie, spontane vena iliaca rupturen en cauda equina syndroom veroorzaakt door DVT. Spontane vena iliaca rupturen zijn zeldzaam en worden gemakkelijk gemist, met 76 casus (64 studies) beschreven in de literatuur. De diagnose moet in het bijzonder overwogen worden bij vrouwen van middelbare of oudere leeftijd, presenterend met hemorragische shock en gelijktijdig linkszijdige DVT. De behandeling van spontane vena iliaca rupturen kan conservatief, endovasculair of open-chirurgisch. Patiënten met chronische vena cava inferior obstructie kunnen zich presenteren met verminderde inspanningstolerantie, zonder enige symptomen of klachten aan de onderste extremiteiten. Succesvolle behandeling met veneuze stents vond plaats in een casus, waarbij hemodynamiek, inspanningstolerantie en kwaliteit van leven verbeterden. Een ander case-report toonde DVT als zeldzame oorzaak van cauda equina syndroom, met een succesvol herstel van beide condities na trombolyse gevolgd door behandeling met veneuze stents. Een tijdige herkenning van DVT als oorzaak van cauda equina syndroom is belangrijk, en biedt de mogelijke overweging van endoveneuze behandeling. Bovenstaande voorbeelden van buitengewone casuïstiek tonen de brede toepasbaarheid en potentie van endoveneuze behandelmethodes.

LIST OF PUBLICATIONS

THIS THESIS

Van Rijn MJE, **Bakas JM**. Treatment of iliofemoral deep vein thrombosis: challenges, opportunities, and future perspectives. *Phlebology Journal*, 2023 Aug; p 26-34 No. 109.

Bakas JM, Lauw MN, Kruip MJHA, Malskat WSJ, van den Bos RR, van Montfrans C, Verhagen HJM, van Rijn MJE. Anticoagulation Management and Recurrent Thrombosis after Venous Stenting for Deep Vein Thrombosis and Post-thrombotic Syndrome. *Eur J Vasc Endovasc Surg*. 2026 Jan 29:S1078-5884(26)00078-X. doi: 10.1016/j.ejvs.2026.01.042. Epub ahead of print. PMID: 41620160.

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LIST OF ABBREVIATIONS

ATTRACT= Acute venous Thrombosis Thrombus Removal with Adjunctive Catheter-directed Thrombolysis trial

BMI= Body Mass Index

CABG= Coronary Artery Bypass Graft

CAVA= Catheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT trial

CaVenT= Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis trial

CDT= Catheter-Directed Thrombolysis

CES= Cauda Equina Syndrome

CFV= Common Femoral Vein

CLOUT= ClotTrieve[®] Outcomes study

CT= Computed Tomography

CTV= Computed Tomography Venography

DFV= Deep Femoral Vein

DM= Diabetes Mellitus

DOAC= Direct Oral Anticoagulant

DUS= Duplex Ultrasound

DVT= Deep Vein Thrombosis/Diepe Veneuze Trombose

ECS= Elastic Compression Stockings

EDV= End-diastolic Volume

EF= Ejection Fraction

ESV= End-systolic Volume (ESV)

ESVS= European Society for Vascular Surgery

FV= Femoral Vein

IDEAL= Ideal Deep Venous Thrombosis study

IL= Inguinal Ligament

IVC= Inferior Vena Cava

IVUS= Intravascular Ultrasound

LIVCS= Left Iliac Vein Compression Syndrome

LMWH= Low-Molecular-Weight Heparin

MCS= Mental Component Summary (SF-36)

MDT= Multidisciplinary Team

MEC= Medical Ethics Committee

MRI= Magnetic Resonance Imaging

MRV= Magnetic Resonance Imaging Venography

MTS= May-Thurner Syndrome

PAOD= Peripheral Arterial Occlusive Disease

PCDT= Pharmacological Catheter Directed Thrombolysis

PC= Packed Cell

PCS= Physical Component Summary (SF-36)

PET= Positron Emission Tomography

PMT= (Pharmaco) Mechanical Thrombectomy

PROMs= Patient-reported Outcome Measures

PTS= Post-thrombotic Syndrome/Posttrombotisch Syndroom

RCT= Randomized Controlled Trial

SEH= Spoedeisende Hulp

SF-36= Short Form Health Survey (36 questions)

STROBE= Strengthening the Reporting of Observational Studies in Epidemiology

SV= Systolic Volume

TIA= Transient Ischemic Attack

TORPEDO= Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion trial

VKA= Vitamin-K-Antagonist

VTE= Venous Thromboembolism

QoL/QOL= Quality of Life

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PHD PORTFOLIO

Name PhD student: Jay M. Bakas
Erasmus MC Department: Vascular Surgery
PhD period: 2021-2026
Title thesis: Life after a venous stent
Supervisors: prof. dr. H.J.M. Verhagen
dr. M.J.E. van Rijn
dr. A. Moelker (in memoriam)
Date defence thesis 24th June, 2026

Courses	Organizer	EC
Stanford University - Writing in the Sciences (2020)	Stanford University	1.40
Stanford University - Medical Statistics I, II, and III (2020)	Stanford University	1.80
Erasmus MC - PhD Introduction session (2022)	Erasmus MC Graduate School	0.20
Erasmus MC - Cardiovascular Biomechanics (2022)	Erasmus MC Graduate School	0.50
Erasmus MC - Scientific Integrity (2022)	Erasmus MC Graduate School	0.30
Biomedical Writing for PhD candidates (LTC course) (2022)	Erasmus MC Graduate School	1.50
Personal Leadership & Communication (2022)	Erasmus MC Graduate School	1.00
Erasmus MC - ESP03 Introduction to Data-analysis (2022)	Erasmus MC	0.70
Erasmus MC - ESP01 Principles of Research in Medicine and Epidemiology (2022)	Erasmus MC	0.70
Erasmus MC - ESP78 Gender and Health (2022)	Erasmus MC	0.70
Erasmus MC - BST01 Review of Mathematics and Introduction to Statistics (2022)	Erasmus MC	1.40
Castor Basic Course (2022)	Erasmus MC	1.00
Young Esser Course (2022)	Esser Masterclass	0.30
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2022)	Erasmus MC	1.50
ATLS: Advanced Trauma Life Support (2023)	Stichting ALSG	1.00

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Courses	Organizer	EC
TTPA: Tips, Tricks and Pitfall Avoidance (2023)	Netwerk Acute Zorg Brabant	1.00
Media contacts for researchers (2023)	Erasmus MC Graduate School	0.10
Science in society (2023)	Erasmus MC Graduate School	0.10
Sustainable Research: Beginner's guide to make your research more environmentally friendly (2023)	Erasmus MC Graduate School	0.10
Presenting skills for PhD candidates (2023)	Erasmus MC Graduate School	0.80
Presentations, congresses, and meetings	Organizer	EC
Erasmus MC - Research Meetings Vaatchirurgie (2022)	Erasmus MC	1.00
Regio IV - Refereeravonden Chirurgie (2022)	Erasmus MC	1.00
Congress - European Venous Forum (2022)	European Venous Forum	1.40
Vascular Rounds (2022)	Stichting Vascular Rounds Zuid-West Nederland	0.30
Venous Academic Research Consortium (2022)	VARC	3.00
Congress - European Society of Vascular Surgery (2022)	European Society of Vascular Surgery	2,20
Congress - Into Veins (2022)	IntoVeins	1,60
Congress - Vascular Interventions Online (2022)	Radcliffe Vascular	0.90
Wetenschapsmiddag - Amphia Ziekenhuis Breda (2022)	Amphia Ziekenhuis Breda	0.80
Wetenschapsdag - Erasmus MC Rotterdam (2023)	Erasmus MC	0.80
Wetenschapsavond - NVIR (2023)	Nederlandse Vereniging voor Interventieradiologie	0.80
Congress - NVvL (2024)	Nederlandse Vereniging voor Longchirurgie	0.80
Presentation Vascular Rounds (2024)	Stichting Vascular Rounds Zuid-West Nederland	0.80
Congress - European Society of Vascular Surgery (2024)	European Society of Vascular Surgery	1.70
Refereermiddag SEH	ETZ Tilburg	0.80

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Prizes	Organizer	EC
Journal of Vascular and Interventional Radiology clinical study certificate: Top 10 selected papers in 2025.	Journal of Vascular and Interventional Radiology	
Venous Stents Placed for Postthrombotic Syndrome: The Role of Inflow Disease on Patency.	Society of Interventional Radiology (SIR) 2026 annual meeting in Toronto	
Other	Organizer	EC
Onderwijs - Klinisch redeneren (vaatchirurgie) voor co-assistenten (2022)	Erasmus MC	1.00
Erasmus MC - Intervention for PhD candidates (2022)	Erasmus MC Graduate School	1.00
Supervision MSc student: Alexander L. Kooiman (2023)	Erasmus MC	2.00
Erasmus MC - PhD Introduction session (2022)		0.20
Peer Review - Journal of Endovascular Therapy (2023)	Journal of Endovascular Therapy	0.50
Peer Review - EJVES (2023-2025)	European Journal of Vascular and Endovascular Surgery	0.50
Abstract reviewer for ESVS Congress (2024 & 2025)	European Society for Vascular Surgery	1.00



Forceline

DANKWOORD

Tijdens mijn coschappen schreef ik een mail naar dr. Marie Josee van Tongerlo-van Rijn. Ik maakte mijn interesse kenbaar in het opdoen van wetenschappelijke ervaring. Achteraf kunnen we deze mail beschouwen als het begin van dit promotietraject.

Beste Marie Josee, uiteraard begin ik het dankwoord bij jou. Toen ik als student aan dit onderzoek begon, had ik niet voorzien wat dit in de toekomst zou brengen. Jouw rol als supervisor is cruciaal geweest voor zowel begin als resultaat. Wetenschappelijk onderzoek komt soms met tegenslagen, echter zorgde jouw betrokkenheid dat het schakelen naar een plan B gemakkelijk verliep. Ontzettend bedankt voor de samenwerking en begeleiding!

Ter nagedachtenis aan dr. Adriaan Moelker (co-promotor en interventieradioloog).

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Voormalig collega's van het Amphia ziekenhuis en Elisabeth-Tweesteden ziekenhuis (ETZ) dank ik voor de leerzame tijd. De collega's van het ETZ natuurlijk ook voor de fanatieke padelwedstrijden en goede broodjes tijdens de weekenddienst. De (oud)opleiders chirurgie (Amphia) en spoedeisende hulp (ETZ) dank ik in het bijzonder voor de mogelijkheid mijn werkzaamheden als ANIOS te combineren met mijn promotietraject: dr. Eelco Veen en prof. dr. Lijckle van der Laan (Amphia ziekenhuis, chirurgie) en drs. Noortje Fransen en drs. Ivo van Ek (Elisabeth-Tweesteden ziekenhuis, spoedeisende hulp).

Na de eerste vlieguren als arts-assistent, besloot ik in 2025 te solliciteren voor de vervolgopleiding tot Radioloog, waarvoor ik werd aangenomen in het Albert Schweitzer ziekenhuis (ASZ) Dordrecht. De lokale opleiders (dr. Nienke Katier en drs. Wouter Dinkelaar) en regionale opleidingscommissie, ontzettend bedankt. Ook dank ik mijn collega's uit het ASZ voor de ontzettend fijne tijd in Dordrecht!

Naast het serieuze en inhoudelijke werk, mag de nodige ontspanning niet ontbreken: zoals de onmisbare bijdrage van mijn vrienden (binnen en buiten de studie). Van een weekendje weg, op vakantie, of op "trappist-/wijnreis". Ontspanning in de vorm van een 1^e, 2^e, en "3^e helft" (en een "avondje NAC" dat telt voor twee). Op het maken van nog heel veel mooie herinneringen!

"The beginning is the most important part of the work" – *Plato*. Papa en mama, bedankt voor jullie liefde en steun (zoals altijd kan ik blind op jullie rekenen). Door twee mensen ben ik op de wereld gezet en drie hebben mij gemaakt tot wie ik ben. Geert, je bent ontzettend belangrijk geweest in mijn leven en dat zal je altijd blijven. Als er een mogelijkheid is dat je vandaag meekijkt, weet ik zeker dat je dit doet.

Lieve Demi, jouw steun en liefde maken alles makkelijker en leuker. Ik kan nog wel even doorgaan, en laten we dat ook vooral doen! Jullie bijdrage is met geen pen te beschrijven.

CURRICULUM VITAE

Jay M. Bakas was born in Delft, the Netherlands in 1996. He graduated from the Montaigne Lyceum The Hague in 2015, and studied medicine in Rotterdam at the Erasmus University Medical Center (2015-2021).



He started a research project beside his study under supervision of dr. Marie Josee E. van Tongerlo-van Rijn at the department of Vascular Surgery of the Erasmus MC Rotterdam. After graduating from medicine in 2021, this research project was continued into a PhD trajectory under supervision of dr. Marie Josee E. van Tongerlo-van Rijn (co-promotor), dr. Adriaan Moelker (co-promotor, *in memoriam*), and prof. dr. Hence J.M. Verhagen (promotor) at the Erasmus MC Rotterdam: resulting in this thesis (2026).

After working at the Amphia Hospital Breda (2023 – 2024) as a surgical resident (not in training) and at the Elisabeth-Tweesteden Hospital in Tilburg (2024 – 2025) as an emergency room resident (not in training), he continued at the Albert-Schweitzer Hospital in Dordrecht as a radiology resident (in training) in 2025.

