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OUTFLOW RECONSTRUCTION OF THE LOWER EXTREMITY IN CHRONIC VENOUS OBSTRUCTIVE DISEASE

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OUTFLOW RECONSTRUCTION OF THE LOWER EXTREMITY IN CHRONIC VENOUS OBSTRUCTIVE DISEASE

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht, op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert, volgens het besluit van het College van Decanen, in het openbaar te verdedigen op vrijdag 6 Juli 2018 om 12:00 uur.

door
Mark Antonius Friedrich de Wolf

Promotor

Prof. dr. C.H.A. Wittens

Copromotor

Dr. R. de Graaf

Beoordelingscommissie

Prof. dr. H. ten Cate (voorzitter)

Dr. M.M.P.J. Reijnen (Rijnstate)

Prof. dr. J.E. Wildberger

Prof. dr. W. Wisselink (VU medisch centrum)

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CHAPTER 1
GENERAL INTRODUCTION

VEINS AND THE VASCULAR SYSTEMS

1

A vascular system is one of the most basic necessities in any complex multicellular organism. Its function is essential to maintain cellular homeostasis, and loss of its function generally leads to death of cells, organs, and possibly the organism as a whole. Anatomically and functionally the circulatory system is comprised of three distinct tubular systems; the lymphatic, the arterial, and the venous system. The main function of the lymphatic vessels is to return interstitial fluid, originating from capillary filtration, more or less directly to the heart. Moreover, it has important immunological functions⁽¹⁾. The arteries' main function is to deliver oxygen-rich blood to the organs, muscles, and other tissues. Oxygen is added to the haemoglobin molecule inside red blood cells in the lungs and is subsequently pumped peripherally by the heart. After delivery of oxygen via capillary diffusion to the tissues, the blood is returned to the heart and lungs via the venous system. In contrast to the arterial system, with the heart pushing blood in the direction of gravity towards the periphery (in case of the lower extremities that is), venous return of blood towards the heart goes against the force of gravity. Flow in the venous system is partly generated by the pressure differences between the periphery and the veins at level of the heart, but the most important generator of flow is the contraction of the (lower) extremity musculature. In the lower extremities the muscles of the calves are paramount for adequate venous function, with every contraction of these muscles blood is expelled upward towards the heart. To negate gravity related venous backflow after such a muscle contraction, the inner lumen of the veins is lined with one-way valves. Therefore, similarly to the arterial system there is only one direction of flow (from the periphery towards the heart) in the healthy venous system. Besides the delivery of oxygen and removal of carbon dioxide from cells, other critical functions of the arteriovenous system include: delivery of nutrients to cells, removal of waste products from cells, transport of cells of the immune system, maintenance of a constant body temperature (thermoregulation), and it functions as a conveyor for hormones (necessary for communication between cells). Dysfunction of the arterial system can be fatal, and indeed stroke and myocardial infarction are among the major causes of death in the Western world.⁽²⁾ Venous pathology in itself can also be fatal in cases of pulmonary embolism, where the circulatory system of the lungs is compromised by a blood clot, generally originating from the peripheral veins.⁽³⁾ However most diseases involving the veins are non-fatal and are located in the vessels of the lower extremities and/or their outflow tracts. This thesis illustrates the treatment of a number of these types of venous pathologies.

CHRONIC VENOUS DISEASE

Signs and symptoms of venous pathology and their underlying pathological causes are represented with the overlapping term “chronic venous disease”. There are two primary

pathological mechanisms underlying chronic venous disease.(4) The first is related to the backflow of blood by gravitational force, termed “venous insufficiency”. For this to happen there needs to be dysfunction of the one-way venous valves. Dysfunction arises when the valve leaflets are damaged. Only in very rare cases venous valves are congenitally underdeveloped or non-developed. Valve damage can be the result of an inflammatory reaction within the vein (as is the case in venous thrombosis), but in most cases there is no clear cause underlying the insufficiency. In those cases the insufficiency is called “primary”, in contrast to “secondary” pathology, which is secondary to another event (usually thrombosis). It is best illustrated by primary varicose vein. In many patients in the Western world varicose veins develop without a clear underlying event, usually gradually and later in life.(5) When examined with duplex ultrasonography, dysfunction of the valves and backflow, i.e. “reflux” of blood, can be found. It is theorised this is because of an inborn relative weakness of the vein walls and/or valves. The reflux induces a rise of venous pressure, which is greatest at the level of the ankle in a standing patient because of the gravitational pull on the column of blood between the ankle and the heart as a whole; i.e. the hydrostatic pressure. The increased pressure then leads to the variety of signs and symptoms related to chronic venous disease via a number of different pathological mechanisms. The second pathological mechanism leading to chronic venous disease is obstruction or occlusion of the lumen of one or more vein segments. In cases of venous obstruction the lumen is reduced and therefore the amount of blood, which can be moved through the segment over a specific time period, is diminished. In cases of occlusion there is absolutely no blood, which can flow through the vessel. In both cases blood needs to leave the extremity via other vein segments (so called “collateral vessels” or “collaterals”), however this is less effective than the original pathway, leading to a higher outflow resistance. This leads to an increase in venous pressure, especially in the caudal veins, and this in turn to the aforementioned signs and symptoms related to chronic venous disease. During exercise this problem increases further as the muscles of the extremity need a higher amount of nutrients and oxygen. Arterial inflow into the extremity therefore increases, and logically the venous outflow also needs to increase. The higher amount of blood however cannot be effectively expelled centrally, leading to relative stasis of blood in the lower extremity. Because of this stasis and its related increased venous pressure, arterial inflow is decreased and muscles tend to fatigue early. In turn this leads to pain in the legs during walking or other forms of exercise. Of special interest is the role of muscle contractions in the extremity during ambulation in patients with either venous insufficiency or obstruction. In insufficiency, in spite of the damaged valves, ambulation will improve venous outflow and thereby decrease venous pressure. This will generally lead to a temporary decrease of symptoms. However, in case of obstruction the increased blood flow during ambulation will be forcefully pumped against the venous network with increased flow resistance, leading to an acute increase in venous pressure distally of any obstruction. Of further note is the fact that in clinical practice both mechanisms, in different severities, may be present in a patient.(5)

DEEP VEIN THROMBOSIS

1 Thrombosis is the formation of a blood clot, which can arise in both arteries and veins. The reasons for clot formation in vessels are encapsulated in Virchow's triad, which states that the combination of stasis of blood flow, endothelial injury, and hypercoagulability can result in thrombosis.(6) In veins thrombosis leads to an acute occlusion of one or more vein segments, with associated acute symptoms of (severe) venous disease. If one or more parts of the localized thrombus break loose from the main thrombus it migrates via the venous system towards the heart and lungs, potentially obstructing a vital part of the lung circulation and possibly leading to death.(7) This is called pulmonary embolism.(3) To prevent this, and to arrest growth of the thrombus, patients experiencing a venous thrombosis are given medication which decreases the ability of blood to form clots, i.e. anticoagulants.(8) There are 3 main groups of anticoagulants in clinical use today for DVT care; vitamin K antagonists (coumarin), heparin and low molecular weight heparin, and the "new oral anticoagulants (NOAC)". (8-11) Because of the complications (patients have a higher tendency for bleeding) associated with these medications, they are generally given temporarily (if medically acceptable, some patients need life-long treatment). During the months following the initial thrombosis the innate remodelling processes of the body tries to recanalise the affected vein segments. This involves an inflammatory process, which can inadvertently lead to fibrosis of the vein wall, destruction of the vein valves and residual intraluminal fibrous strands. Therefore thrombosis may lead to both chronic venous obstruction and valvular insufficiency. To combat these complications, thrombosis patients are treated using compression therapy, generally in the form of compression stockings and bandages. This treatment was shown to prevent thrombosis associated chronic venous disease (i.e. post-thrombotic syndrome) in a great percentage of patients.(12-14) As stasis of blood may lead to thrombosis and muscular contraction prevents stasis, patients are also advised to start mobilisation quickly after the thrombosis. Therefore the treatment of deep vein thrombosis (DVT) consists of pharmaceutical anticoagulation, compression therapy and quick ambulation.

THE POST-THROMBOTIC SYNDROME

The most important cause of venous obstruction is the post-thrombotic syndrome (PTS). In a certain percentage of patients (up to 50%) after a DVT a specific type of chronic venous disease develops some months to years post-DVT.(12, 14-16) This can be explained by the fact that the therapy used to treat DVT is not particularly effective in preventing the long term vein damage caused by the innate inflammatory process associated with a DVT. Because of this the damage to the vein wall and the intraluminal scarification become an irreversible outflow obstruction, in combination with the valve

destruction, this can lead to chronic increased venous pressure and its associated symptoms.(17, 18) This is called PTS. Anatomically, PTS is characterised by veins in which the intraluminal diameter is reduced (stenosis), the intraluminal space is filled with fibrous strands (trabeculation) creating multiple canals through the length of the vein, the vein wall is fibrosed, and vein valves are damaged or completely (functionally) absent.

Both the incidence of PTS and its severity are associated with the location of the post-thrombotic damage.(19) Generally proximal/cranial DVTs, those located at the level of the vena cava, iliac veins or the common femoral vein (CFV), are associated with higher incidence and severity of PTS.(19-21) This can be explained by the fact that those veins are the ones responsible for the outflow of the greatest volume of venous blood. In contrast, at the level of the calve and upper leg there are generally multiple veins running more or less parallel with each other.(22) Therefore in cases of obstruction at levels below the CFV flow is diverted upwards via other non-obstructed veins; i.e. collaterals. These collateral networks are generally associated with a higher degree of venous resistance, leading to increased venous pressure distally of the obstruction and associated symptoms of chronic venous disease. Blood however does have the ability to leave the lower extremity, so the cardiovascular circulation is maintained. This is in stark contrast to arterial obstruction and occlusion, which may lead to (acute) ischaemia of tissue and cellular necrosis. Given the incidence of DVT being 1-2 per 1.000 individuals yearly and up to 50% of these patients developing chronic complications, PTS is a very significant cause of chronic venous disease, its associated morbidity, and health-care costs.(23, 24) Historically its treatment has been primarily based on compression therapy, and to a lesser extend medication.(12-14, 25, 26) However this treatment is not aimed at treating the underlying obstruction of the veins. In very select patients, those most severely affected by PTS, surgery was performed in a number of very specialized centres worldwide.(27, 28) Surgery consisted of the creation of artificial collaterals, e.g. veno-venous bypasses. Clinical and haemodynamic long-term effectiveness of this type of surgery however was suboptimal. Therefore alternatives were needed.

ILIAC VEIN COMPRESSION SYNDROMES

The second main cause of venous obstruction is pressure onto the vein from extra luminal sources. The most important source of pressure are the arteries in the vicinity of the veins, especially at the level where arteries cross the veins. And of these arterial crossings, the right common iliac artery traversing the left common iliac vein (CIV) is the most frequent cause of pathology. As the CIV runs across the bony vertebral corpus, the vein may be compressed between the common iliac artery and the vertebra. Signs and symptoms associated with this iliac vein compression are similar to other types of chronic venous disease. The combination of this clinical symptomatology and the anatomical compression of the CIV is termed May-Thurner syndrome (MTS). MTS

1 was first described in the early nineteen hundreds, and was recognized as the cause for the predominant occurrence of DVT in the left lower extremity compared to the right leg.(29) A study in subjects without venous disease showed compression of the CIV to be present in the majority of subjects; 66% of patients had a compression of >25% and 24% showed compression of the CIV to be greater than 50% (in many studies a compression of >50%, in combination with clinical symptoms, is considered to be an indication for stent placement, see below).(30, 31) Other causes of iliac vein compression include pressure on the vein by nearby structures such as tumours, arterial aneurism, haematoma etc. The overlying term used to describe these compression syndromes is iliac vein compression syndrome (IVCS).

RECANALISATION, VENOPLASTY AND STENTING

Because the lumen is totally clogged in many patients and severely diminished in the rest the first thing to do is to reopen the lost lumen. Recanalisation without the use of open-surgery is performed by use of various guidewires and catheters, introduced into the deep venous system via an introduction sheath in the CFV, femoral vein or popliteal vein. Recanalisation is followed by increasing the newly created lumen by use of balloons. In the 1960's it was shown by Charles Dotter that tubular structures could be expanded by use of intraluminally delivered balloons, which is termed angioplasty in case of blood vessels.(32) In the venous system this technique can also be used. However this "venoplasty" by itself is not effective as recollapse of the post-thrombotically damaged or compressed vein occurs quickly after treatment.(33-35) Therefore a device is needed to keep the treated vein segment open on the long term. A stent is such a device. For vascular use these are generally made from some type of metal. Stents are implantable via a catheter into hollow organs, in this case veins. The stent delivers a constant pressure into the vein wall, thereby keeping the vein open. By use of the combination of guidewire recanalisation, venoplasty and stenting of the occluded or obstructed veins physicians aim to reopen the veins and keep these open over a long period. This treatment is thought to normalise venous haemodynamics, decrease venous pressure and thereby signs and symptoms of venous disease can diminish.

DEDICATED VENOUS STENTS

Historically stenting and angioplasty first gained popularity in arterial and cardiac use. Because of the similarities between arteries and veins the same stents as used in arteries have been used in the venous system.(36) In many studies this has shown very favourable results, however a number of complications related to the use of these stents have nevertheless been identified.(30, 36-40) A number of important differences

between arterial diseases, i.e. arteriosclerosis, and venous pathology exist. Firstly, even though arteriosclerotic damage can frequently be found at many locations in a patient's arterial system, the stenotic lesions which are treated by stenting are generally only several centimetres in length. In contrast, in patients who suffered a DVT involving their iliac veins the post-thrombotic damage frequently extend from the CIV to the level of the knee (>50 centimetres) or even the calve veins. Even though only the CIV, external iliac vein (EIV) and CFV are generally eligible for stenting, this still involves >20 centimetres of vein tract.⁽⁴¹⁾ Secondly, veins have a greater diameter compared to their corresponding arteries (e.g. the CIV compared to the common iliac artery). Thirdly, veins are more flexible and more subject to external forces compared to arteries, because of the lack of a thick muscular layer in the vessel wall and the lower intraluminal pressure. And fourthly, the rigidity and inward pushing force of atherosclerotic lesions is less compared to fibrotic post-thrombotic lesions. Because of these specific qualities of the venous system, the ideal venous stents has the following characteristics; adequate length and diameter, maximal flexibility, great radial force, and non-crushability.⁽⁴²⁾ A number of companies have recently developed dedicated venous stents, and some of these have already become available for clinical use.^(42, 43)

ENDOPHLEBECTOMY AND ARTERIOVENOUS FISTULA

Stent implantation is generally performed in the iliac veins and the CFV.⁽³⁰⁾ Frequently the femoral, deep femoral, popliteal and calve veins are also affected by post-thrombotic damage.⁽⁷⁾ As flow through these vein segments into the stents is reduced and relative stasis of blood can cause clot formation (Virchow's triad), there can be an increased risk of instent-thrombosis and loss of patency. Stenting can be relatively safely done into the CFV when inflow from one of the two major inflow vessels of the CFV, the femoral and deep femoral vein, is adequate. However if both inflow vessels are significantly affected by post-thrombotic damage, the risk of stent occlusion increases. This is partly because of blood flow being diverted to collateral veins, however at the level of the CFV there are less collaterals available. Indeed the CFV is the segment of the venous systems where a number of important collateral vessels of the lower extremity converge to direct flow though the inguinal ligament into the iliac veins. As already stated a number of different canals can be present in a post-thrombotic vein, all creating flow towards the heart, but not necessarily interconnecting. Flow from different side branches of the CFV may flow through different canals within the CFV. When a stent is placed in one of these canals the others are compressed, and blood flow might cease in those canals. Therefore, by stenting a vein the inflow from side branches can be severely diminished, which is generally not an issue in the iliac tract. However at the level of the CFV, stents placed over the orifice of one of the major inflow vessels can totally obstruct flow via these vessels. This can be rather problematic when a significant fraction of the total venous outflow of the leg is obstructed by the stent. This is the reason some authors

advocate the use of a surgical desobstruction of the CFV, termed an endophlebectomy or endovenectomy.⁽⁴⁴⁻⁴⁷⁾ This guarantees all canals from all side branches at this level to flow into one channel, and thereby all flow can be concentrated into the stents which are placed in the vein section just cranially of the endophlebectomy. However, the combination of the iliac stenting and the surgical trauma of the endophlebectomy creates a highly thrombogenic environment, therefore measures must be taken to reduce the risk of thrombosis of the stented and endophlebectomized vein segments. For this reason the creation of an ancillary arteriovenous (AV)-fistula can be created (besides the use of anticoagulants). The AV-fistula connects the artery and the vein, and because of the great difference in pressure in both systems, flow through the vein is considerably increased. As stated before, higher flow equals a decrease in risk of thrombosis.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to enlighten the indications, technique and clinical effects of venous reconstruction by use of percutaneous transluminal angioplasty (PTA) and stenting, supported in some cases by endophlebectomy and temporary AV-fistula creation, in a population of patients suffering from chronic venous obstructive disease.

Chapter 2 describes the post-thrombotic syndrome from an epidemiological point of view. This review of literature gives an overview of current insights on the incidence of PTS and its risk factors. PTS is a relatively common disease in Western countries. Numerous risk factors are currently known, and there is ongoing research into new ways to predict and prevent PTS development.

Our first experience of PTA and stenting in Maastricht are described in *chapter 3*. We described the techniques we used for diagnostic imaging and the intervention in the patients treated between 2009 and February 2012. Moreover, clinical outcome, including patency rates and the effect on symptoms, is described. In this chapter the effect of the “old” non-dedicated stents is described. Also a number of the specific stent-related problems, such as kinking and stent compression, are described. Following the treatment of the patients described there, we switched to dedicated venous stents.

In *chapter 4* our initial experience with one such dedicated venous stent is described. We chose to primarily use the sinus Venous stent (OptiMed, Ettlingen, Germany) in both PTS and IVCS patients. The sinus Venous is a nitinol stent. Nitinol is a specific kind of memory metal frequently used in stent designs. This stent is characterised by a high radial force and a high flexibility. Moreover it is available in diameters and lengths adequate for the venous system. This chapter describes the specific technique used for placement of the stent, and the clinical outcome for both PTS and IVCS cases.

In a minority of patients with chronic venous obstructive disease both lower extremities are affected. This can be because of two-sided compression syndromes, but in most cases the source is bilateral DVT. Frequently the vena cava inferior is also affected. Treatment in these cases necessitates a specific technique as both iliac tracts and the inferior vena cava need to be stented simultaneously. Reconstruction the iliac confluence is technically demanding. The technique we use to treat this is described in *chapter 5*, as is its clinical outcome. It is noteworthy that our technique differs from many other available studies. We chose to use balloon-expandable stents at the level of the confluence in conjunction with self-expandable stents proximally and distally from the balloon-expandable stents.

As already stated above, in a significant number of patients not only the CFV is severely damaged by the DVT, but also both main inflow vessels (femoral and deep femoral vein). In those cases we chose to complement the PTA and stent treatment with an endophlebectomy and a temporary AV-fistula creation. The specific clinical indications for this hybrid surgery and the preoperative diagnostic tests performed are illustrated in *chapter 6*. The hybrid surgical technique and its clinical outcome is described in *chapter 7*. The hybrid technique is generally well tolerated and an effective way to reconstruct the venous outflow, however a number of specific complications are associated with it, these are all described in these chapters.

In *chapter 8* the totality of our first 7 years of experience with deep venous reconstructions is reported. In contrast to the earlier chapters a more generalised view is used to describe the clinical outcome of all patients treated in our centre by use of PTA and stenting.

Finally in *chapter 9* an indepth view is presented on the most important complication of deep venous reconstructions; thrombosis of the treated vein segments. Recent advances in the treatment of acute DVT have led to the increasing use of catheterbased techniques for quick thrombus removal. Generally two types of techniques are available; thrombectomy and thrombolysis techniques. We have used the latter to treat the instant thrombus of patients in whom vein segments reoccluded after stenting.

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CHAPTER 2

INCIDENCE AND RISK FACTORS OF THE POST-THROMBOTIC SYNDROME

M.A.F. de Wolf^{1,2}

C.H.A. Wittens^{1,2,3}

S.R. Kahn⁴

¹ Department of Surgery, Maastricht University Medical Centre

² School for Cardiovascular Diseases (CARIM), Maastricht University, Maastricht, The Netherlands

³ Department of Vascular Surgery, Aachen University Hospital, Aachen, Germany

⁴ Division of Internal Medicine, McGill University and Center for Clinical Epidemiology, Jewish General Hospital, Montreal, Canada

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ABSTRACT

Annually 1 – 2 in every 1000 adults will develop a deep venous thrombosis of the lower extremity. A third to half of these patients will develop the post-thrombotic syndrome (PTS). However, predicting which patients will develop the PTS remains elusive. Ipsilateral thrombosis recurrence seems to be the most important risk factor. Moreover, residual venous occlusion and valvular reflux seem to predict PTS incidence to some degree. Laboratory parameters, including D-dimers and inflammatory markers, have shown promise in predicting development of the PTS in patients and are currently under investigation. Creating a model based on all combined risk factors and patient characteristics might aid in risk stratification in individual patients.

INTRODUCTION

Annually, approximately 1 – 2 in every 1000 adults will develop a deep venous thrombosis (DVT) of the leg, slightly more than half of these are hospital-acquired.¹ Apart from the acute symptoms, consisting of a painful, swollen, red and warm extremity, at least onethird of these patients will develop the post-thrombotic syndrome (PTS). PTS encompasses a great range of symptoms varying from relatively mild signs (slight swelling, venous eczema, pigmentation and minor complaints) to the gravest of venous symptoms: i.e. severe oedema, venous claudication, chronic pain and recurrent ulcers. PTS incidence in the DVT population is generally accepted to be between 20% and 50%. Reported percentages depend mostly on patient characteristics, follow-up duration and treatments used (Table 1).^{2 – 35} In 5 – 10% of DVT patients, severe PTS, characterized by chronic debilitating symptoms, will develop.^{6,10,25} Symptoms of PTS normally arise within the first year post-DVT, thereafter only PTS severity rises.²⁷ Quality of life (QoL) is dramatically decreased in these most severe cases, with QoL scores comparable with patients with congestive cardiac failure or chronic obstructive pulmonary disease.^{18,36,37} Furthermore, enormous socioeconomic costs are associated with PTS, especially when patients develop chronic venous ulcers.^{38 – 40}

PATHOPHYSIOLOGY

The PTS can be seen as a special form of chronic venous insufficiency, with a clearly definable starting point at the moment of the first DVT and a generally rapid progression towards venous complaints and symptoms, i.e. high CEAP (clinical, aetiological, anatomical and pathological elements) (Table 2), VCSS (Venous Clinical Severity Score) and Villalta (Table 3) scores. The basis of PTS pathophysiology is formed by a triad of venous obstruction by residual thrombus or scarification of venous tracts, venous insufficiency due to valve destruction and reduced mobility leading to impairment of calf muscle pump function. Recent and current studies are clarifying the role of the inflammatory system and the manner of thrombus fibrin degradation in post-DVT vein tracts.^{41 – 44} Ultimately, these changes in the venous system of the lower extremity might all lead to impaired venous outflow, venous hypertension and finally abnormal capillary perfusion.

Table 1 Incidence of the post-thrombotic syndrome² – 35

Author	Year	No. patients	Mean FU time (years)	PTS (%)	Severe PTS (%)	Ulcers (%)	Recurrent DVT (%)	Comments
O'Donnell et al.	1977	21	>10	100	NR	86.0	42.9	Strong selection bias
Strandness et al.	1983	61	3.25	67	23	4.9	NR	Abstract only
Widmer et al.	1985	278		16	NR	8.0	14	Abstract only
Lindner et al.	1986	47		79	NR	4.3	NR	Abstract only
Monreal et al.	1993	79		56	20	NR	NR	Abstract only
Heldal et al.	1993	76	7.4	42	21	NR	NR	Abstract only
Eichlisberger	1994	223	13	39	NR	9.8	NR	Abstract only
Beyth et al.	1995	124	6-8	42	NR	NR	15.0	Abstract only
Johnson et al.	1995	78		41	32	2.6	NR	
Prandoni et al.	1996	355		29	9	NR	30.0	
Franzeck et al.	1996	39	12	36	8	3.0	24.0	
Brandjes et al.	1997	194		31/70	11/23	1/3	15/13	ECS versus no ECS
Prandoni et al.	1997	528		30	5	NR	19.0	
AbuRahma et al.	1998	105		44	NR	6.7	21.8	
Biguzzi et al.	1998	51	3.9	59	4	NR	NR	Abstract only
Masuda et al.	1998	54		57	0	0.0	9.0	
McLafferty et al.	1998	37	3.4	38	3	2.7	0.0	
Haenen et al.	1999	82	10	73	34	5.0	12.0	
Holmström et al.	1999	265	5-14	76	NR	4.2	27.5	
Ginsberg et al.	2000	91		5	NR	NR	NR	
Saarinen et al.	2000	26		73	NR	NR	NR	Abstract only
Mohr et al.	2000	1527	7.3	27	NR	3.7	NR	
Ginsberg et al.	2001	202		17	NR	0.0	NR	
Ziegler et al.	2001	162	6.6	82	7	7.0	30.0	
Gabriel et al.	2004	135		62	NR	0.0	7.4	
Stain et al.	2005	406		43	1	1.4	6.4	
Roumen-Klappe et al.	2005	93		56	33	0.0	22.6	
Kahn et al.	2005	145	2.2	37	4	1.4	1.4	
Schulman et al.	2006	897	10	56	6	NR	29.0	
Tick et al.	2008	1668		25	7	3.0	NR	
Gonzalez-Fajardo et al.	2008	165		65	24	NR	26.1	
Aschwanden et al.	2008	169	3.2	17	1	0.0	NR	
Roumen-Klappe et al.	2008	69		88	NR	0	NR	
Kahn et al.	2008	387	2	43	3	1.3	9.9	

NR, not reported; FU, follow-up; ECS, elastic compression stockings; Abstract only, only the abstract of the paper was available to the authors; PTS, post-thrombotic syndrome; DVT, deep venous thrombosis.

Table 2 CEAP Classification, adapted from Eklöf et al.⁹⁷

Clinical manifestations of the revised 2004 CEAP classification		Attributed signs and symptoms
CEAP C ₀		No visible or palpable signs of venous disease
CEAP C ₁		Telangiectases or reticular veins
CEAP C ₂		Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more
CEAP C ₃		Oedema
CEAP C _{4a}		Pigmentation or eczema
CEAP C _{4b}		Lipodermatosclerosis or atrophie blanche
CEAP C ₅		Healed venous ulcer
CEAP C ₆		Active venous ulcer
CEAP, clinical, aetiological, anatomical and pathological elements		

CURRENT TREATMENT OPTIONS

The cornerstone of PTS prevention remains the use of elastic compression stockings (ECS) after a symptomatic DVT event. Studies on long-term use of ECS after a proximal DVT have shown a highly significant reduction in both mild/moderate PTS and severe PTS.⁴⁵ Therefore, it is generally recommended to prescribe below-knee ECS with a pressure gradient of 30–40 mmHg to patients with symptomatic proximal DVT.⁴⁶ Use of lower-pressure gradient stockings might increase patient satisfaction and therapy compliance; however, evidence on the lowest amount of pressure needed to prevent PTS is currently unavailable. Also, ECS treatment duration is controversial. Current guidelines advocate the use of ECS for two years or longer after an initial thrombotic event; however, Aschwanden et al.³ recently showed no added effect of prolonging ECS treatment after six months for prevention of skin changes and PTS symptoms, suggesting that a decrease in treatment duration is feasible. Moreover, Roumen-Klappe et al.²⁸ suggest multilayer compression bandaging in the acute phase of DVT to have no effect on the development of the PTS compared with delayed compression therapy with stockings. Starting treatment solely with elastic stockings within two weeks post-DVT thus seems feasible.

Prevention of PTS is now the major focus of trials researching catheter-directed thrombolysis to treat proximal DVT (e.g. the Scandinavian CAVENT trial, the American ATTRACT trial and the Dutch CAVA trial).^{47–49} Thrombolysis in the acute phase of DVT has been proposed to reduce long-term venous occlusion. Furthermore, rapid recanalization of venous tracts may reduce valve damage and avert deep venous insufficiency. Short-term studies have shown the safety and

feasibility of this treatment modality; however, the long-term effects on PTS development are currently unknown.^{50 – 53}

Table 3 Villalta score, adapted from Kahn et al.⁹⁸

Symptoms and clinical signs	None	Mild	Moderate	Severe
<u>Symptoms</u>				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paraesthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
<u>Clinical signs</u>				
Pretibial oedema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
<u>Hyperpigmentation</u>	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent	Present		

PTS, post-thrombotic syndrome. Points are summed into a total score (range 0 – 33). PTS is defined by a total score of 5 or the presence of a venous ulcer. PTS is classified as mild if the Villalta score is 5 – 9, moderate if the Villalta score is 10 – 14 and severe if the Villalta score is 15 or a venous ulcer is present. To use the Villalta score as a continuous measure, it is recommended that patients who meet criteria for severe PTS based solely on the presence of an ulcer (i.e. total Villalta score is 15) be assigned a score of 15.

During the last two decades a number of invasive treatments have been proposed to treat both deep venous insufficiency and persistent occlusion after a thrombotic event. A number of surgical procedures to treat venous valve insufficiency currently exist: internal and external valvuloplasty,⁵⁴ external banding,⁵⁵ the Maleti neovalve⁵⁶ and axial vein transfer.⁵⁷ Valvuloplasty is preferred by most authors. However, in a great number of patients valvuloplasty is not a viable option, due to destruction of the valve leaflets during the recanalization process in post-thrombotic legs. Persistent post-DVT occlusions are now being recognized as being of importance and treated in a number of specialized centres by angioplasty and stenting. Mid- and long-term follow-up show good results with primary patency rates of approximately 80% two years post-stenting and a clinically significant decrease in PTS symptoms;^{58 – 60} however, randomized controlled trials of these treatments are lacking. In general, interventional treatment is only offered at select centres with expertise in these techniques to patients with severe persistent symptoms after the initial DVT.

In light of the limitations of the current treatment options, identification of risk factors for the development of PTS remains of greatest importance. Likewise, identification of high-risk patients will be needed in selecting patients for treatment with catheter-directed thrombolysis in the future.

RISK FACTORS

Age

Differences between young and old patients might underlie differences in PTS incidence, though no clear mechanism has been postulated yet. Changes in the vein wall, hormonal factors, innate thrombus lysis, inflammatory response to thrombosis and mobility/calf muscle pump function might all differ by age. Advancing age has been clearly shown to be a risk factor for DVT, with incidence being very low in children (ranging from 34 to 58 cases of venous thromboembolism per 10,000 hospital admissions in children of 18 years of age) and increasing steadily to 3.1 per 1000 by the age of 85 – 89 years.^{61,62} However, the relation between age and incidence of PTS remains controversial. Conflicting reports in the literature have been put forward; some authors have described a positive correlation,^{17,30,31,63 – 65} some reported no correlation¹⁷ and some even a lower incidence of PTS in older patients.³³ An increase of 0.3 points in the Villalta score per 10-year age increase was found by Kahn et al.,⁶⁵ whereas Stain et al.³¹ reported an odds ratio (OR) for PTS development of 1.2 for every 10-year age increase. Moreover, Schulman et al.³⁰ showed age above 60 years to be associated with a higher proportion of proximal DVT (58% versus 42%, $P = 0.001$) and a higher DVT recurrence rate (31% versus 25%, $P = 0.049$), compared with younger patients, both of which are independent risk factors for the development of PTS. A relationship between severity of PTS and age, however, has not been noted.¹⁷

Obesity

Increased body weight has been proposed to lead to poor calf muscle function via lack of physical exercise, increased venous pressure and promotion of venous reflux. Obesity has indeed been associated with an increased risk of PTS.^{5,17,31,33,64,66} A 1.5-fold increase in PTS incidence in patients with a body mass index (BMI) ≥ 30 kg/m² has been described.³³ An increase in Villalta score of 0.14 and 0.16 per 1 kg/m² increase in BMI has been described by Kahn et al.^{17,65} in two studies. Furthermore, a higher BMI has been associated with less favourable QoL scores in PTS patients.¹⁸

Sex differences have historically been of great interest within the whole spectrum of venous pathology. However, underlying causes of such differences have been poorly understood. These might include hormonal, mechanical or anatomical dissimilarities. Increased incidence of PTS has been described in both males and females.³³ Stain et al. found male gender to be a weak predictor of PTS occurrence (OR 1.6) and also found

an increased incidence of DVT recurrence in men, which is an independent risk factor for PTS development.³¹ However, a greater number of studies found PTS to be more prevalent in women.^{33,65} Female sex had no effect on two-year QoL changes in post-DVT patients, including PTS patients.¹⁸

Table 4 Summary of risk factors for PTS

Risk factor	Correlation with PTS incidence	Comment
Age	+	Also correlates with DVT recurrence risk
Obesity	+	
Female gender	+	Conflicting evidence
Provoked (vs Unprovoked) deepvenous thrombosis	±	Strong risk factor for venous thromboembolism recurrence
Ipsilateral recurrence	++	Also correlates with severity of PTS
Thrombus location (proximal versus distal)	+	Also correlates with severity of PTS
Residual occlusion	++	
Residual reflux	++	Deep and superficial reflux
Insufficient quality of anticoagulant therapy	+	Conflicting evidence
Thrombophilia	±	Factor V Leiden or the G20210A prothrombin gene mutations
D-Dimer	+	
Inflammatory markers	+	Currently being evaluated

PTS, post-thrombotic syndrome; DVT, deep venous thrombosis Risk factor's relation with PTS incidence: ++ strong correlation, + moderate correlation, ± mostly unclear or no correlation

Unprovoked vs. provoked DVT

While surgery and trauma are associated with a high incidence of provoked DVT (ORs as high as 21.7 and 12.7, respectively⁶⁷), unprovoked DVT on the other hand might be an indication of an underlying hypercoagulable state that could lead to a higher incidence of recurrent thromboembolic events and PTS. However, a difference in the incidence of PTS after unprovoked versus provoked DVT has not been noted.^{5,11,31,68,69}

Ipsilateral DVT recurrence

Ipsilateral recurrent thrombosis is common in DVT patients (Table 1). Two or more thrombotic events in the same extremity have been shown to increase the incidence of PTS,^{4,12,25,26,31,35,63} and previous ipsilateral thrombosis was associated with a 1.78-point increase in Villalta score.^{18,65} Conversely, presence of PTS was associated with a 6- to 11-fold increased incidence of recurrent DVT in patients treated with anticoagulants.¹² This might be explained by the findings of Young et al.⁷⁰ who

showed an increased risk (hazard ratio 2.2) of DVT recurrence in limbs with residual thrombosis, as residual thrombus is also a known predictor of PTS. The mechanism by which DVT recurrence increases PTS incidence and/or severity most likely relates to aggravation of local venous damage and worsening of venous reflux via valvular destruction and extension of residual occlusion of affected vein segments. Kahn et al.⁶⁵ showed a 9.9% incidence of recurrent thrombosis during two years after treatment of DVT with anticoagulants; predictors of recurrence were cancer-associated venous thrombosis, unprovoked venous thrombosis, proximal (versus distal) thrombosis, symptomatic pulmonary embolism at study enrolment and male gender. Higher incidences of recurrence in patients with proximal DVT and in males have also been noted after longer patient follow-up.^{26,30,65} Increased contralateral recurrence has also been noted in a number of studies, probably via systemic vein wall defects, blood hypercoagulability or body habitus.^{12,35} A lower incidence of recurrence was seen after DVT provoked by surgery or trauma, conceivably because no underlying systemic venous aberrations were present.²⁶

Thrombus location

In many studies, proximal thrombi in the deep venous system (popliteal, femoral, common femoral and iliac veins) have been associated with a worse clinical and haemodynamic outcome and lower QoL scores than distal thrombi (peroneal, tibial, gastrocnemial, and soleus veins).^{9,15,18,23,31,33,65,71,72} Controversy remains, however, as some studies did not find this correlation.^{25,63} Kahn et al. found a PTS incidence of 52% in patients with proximal DVT versus

41% in distal DVT, and a 2.23-point increase in Villalta score with proximal versus distal DVT.^{18,65} Similar findings were shown by Holmström et al.¹⁵ QoL scores were also lower in patients with proximal versus distal DVT.¹⁸ Van Ramshorst et al.⁷³ showed thrombus extent to correlate well with the number of refluxing vein segments at follow-up, but no association was shown for clinical severity. Eichlisberger et al.⁷ showed a greatly increased incidence of PTS in patients with four-level thrombosis compared with those with popliteal vein thrombosis only (55% versus 4%, respectively) at 13 years after the initial DVT, and Tick et al. showed a 1.3-fold increase in PTS incidence with iliofemoral as compared with popliteal thrombosis.³³

Residual occlusion

Incomplete recanalization of thrombosed venous tracts is thought to impair the outflow of post-DVT extremities, thereby promoting venous hypertension. Johnson et al.¹⁶ showed residual occlusion to be present in 80% of post-thrombotic limbs and reflux to be present in 83% (in 65% of limbs both occlusion and reflux were present). It takes a mean of 3.4 +5.9 months to achieve 50% recanalization after DVT.⁷² Prandoni et al.⁷⁴ found a relative risk for PTS development of 1.56 with the presence of residual vein thrombosis, and 1.69 if both residual vein thrombosis and popliteal vein reflux were present. In another study, they found a hazard ratio of 2.4 for recurrent

thromboembolism in patients with residual thrombosis compared with those with complete recanalization.⁷⁵ This was confirmed in another study that showed the risk of DVT recurrence and mortality was increased in patients with residual occlusion after DVT (hazard ratios 2.2 and 3.9, respectively).⁷⁰ However, controversy remains as Haenen et al.¹³ found no relation between non-compressibility or the combination of reflux and non-compressibility and PTS. Kahn et al.¹⁷ found comparable results. Furthermore, the proportion of venous occlusion was reported to be the same in patients with CEAP scores of Co – 3 and C4 – 6.⁷⁶

Residual reflux

Loss of venous valve function due to thrombosis has been proposed as one of the main pathological pathways by which PTS develops. Indeed, it has long been shown that reflux in the deep veins of the affected limb correlates well with incidence and severity of PTS.^{13,76,77} Yamaki et al.⁷⁶ showed peak reflux velocity in the popliteal and femoral vein on duplex to correlate highly (OR 60.32 for popliteal vein and 25.77 for femoral vein) with severity of chronic venous insufficiency. Haenen et al.¹³ showed reflux in the proximal deep veins to be associated with worse CEAP scores (Table 2), but no such relation was shown for reflux in superficial veins and distal deep veins. In a second study, the same group showed superficial venous reflux to be the most important risk factor for onset of PTS symptoms and 64% of patients with severe PTS were shown to have a combination of superficial and deep reflux.⁷⁸ A combination of deep and superficial reflux therefore seems to underlie PTS pathogenesis.

Insufficient quality of anticoagulant therapy

Vitamin K antagonist treatment is still one of the cornerstones of DVT treatment.⁴⁶ Insufficient quality of anticoagulation might inhibit the recanalization process and worsen clinical outcome in the affected limb. Ziegler et al.³⁵ indeed showed this relation. They described insufficient anticoagulation measurements in half of the patients suffering from venous ulcers. More recently an increased incidence of PTS (OR 2.71) was described in patients whose international normalized ratio (INR) level was below 2.0 for >50% of the time.⁶⁴ Moreover, longer treatment duration with oral anticoagulants significantly reduces the risk of recurrent thrombosis, which is an important risk factor for PTS.¹⁵

Thrombophilia

The presence of factor V Leiden or the G20210A prothrombin gene mutation has been shown to increase the risk of a first venous thrombosis.^{79,80} Moreover, in family members of patients with one of these mutations, an OR of 1.68 was found for DVT incidence.⁸¹ There is conflicting evidence on the role of these thrombophilia markers on PTS incidence. Kahn et al.¹⁷ showed factor V Leiden or the prothrombin gene mutation to be independently associated with a decreased incidence of PTS (OR 0.33) and a 1.6 decrease in Villalta score. However, in another study by the same group,

these results could not be replicated and the same is true for a number of other recent studies.^{31,33,63 – 65}

D-dimer

Elevated plasma D-dimer concentration predicts both first and recurrent DVT events.^{82 – 88} Stain et al.³¹ showed D-dimer levels to be positively associated (OR 1.9) with PTS incidence. The recent finding that D-dimer was strongly reducible by vitamin K antagonists supports this assumption and reflects the fact that increased INR seems to protect against PTS development.⁸⁹ Latella et al.⁹⁰ showed that increased D-dimer levels were associated with occurrence of PTS in both DVT patients treated with and without vitamin K antagonists, and the association was strongest in those not currently treated (OR 3.79).

Inflammatory markers

Recently, a number of studies have focused on the role of inflammatory cytokines and adhesion molecules in the development of PTS. These include interleukin 6, 8 and 10 (IL-6, IL-8 and IL-10), C-reactive protein (CRP), monocyte chemotactic protein-1 (MCP-1), intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Studies were based on the hypothesis that the inflammatory response to DVT leads to vein wall abnormalities. PTS patients were shown to have a 1.6-fold increase in mean IL-6 level and a trend towards higher median levels of IL-6 four months after DVT diagnosis.⁴⁴ Roumen-Klappe et al. showed that IL-6 and CRP levels measured on the day of DVT diagnosis did not correlate with Villalta score one year post-DVT and only weakly correlated with CEAP classification one year post-DVT, but strong associations were seen between these markers and venous outflow resistance 90 days post-DVT (which in itself correlates with PTS incidence after 1 year), and in the case of IL-6, Porter's thrombosis score (based on thrombus extent and site involvement).^{43,91} ICAM-1 levels are also associated with PTS.^{44,92} No correlations between PTS and IL-8, IL-10, MCP-1 and VCAM-1 were shown.^{43,44} An association between inflammatory markers and reflux was not seen, supporting the notion that the inflammatory response may act on vein wall characteristics rather than venous valves.^{43,44,92} However, studies in animal models strongly suggest a role of inflammatory pathways in the development of venous valve degradation in chronic venous insufficiency, which indicates that secondary damage due to pathological haemodynamics post-DVT might contribute to PTS progression rather than initiation.^{93,94} Moreover, increased plasma levels of IL-6, IL-8 and MCP-1 have been shown to be increased in patients with recurrent DVT, which is an independent risk factor for PTS development.⁹⁵ The value of inflammatory markers in the prediction of PTS is currently being evaluated in a large prospective study.⁹⁶

CONCLUSION

General interest and awareness of the PTS have recently been stimulated by improved standardization of PTS measurement and the emergence of new potential treatment modalities such as new oral anticoagulants, catheter-directed thrombolysis and deep venous stenting procedures. However, effective stratification of the risk for progression to PTS in patients presenting with a first or recurrent DVT remains elusive. Recurrence of thrombosis in the same extremity as the index DVT, with resultant increased venous damage, seems to be one of the

most important risk factors for PTS development. Residual venous occlusion and valvular reflux, signifying venous damage, also seem to predict PTS incidence to some degree. Based on promising preliminary work, the value of D-dimer and inflammatory marker levels as a means to predict PTS is currently being investigated. Work to develop a future model that combines the above factors together with patient characteristics could provide a useful tool for stratifying risk of PTS development in individual patients with DVT.

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CHAPTER 3

MINIMALLY INVASIVE TREATMENT OF CHRONIC ILIOFEMORAL VENOUS OCCLUSIVE DISEASE

Mark Antonius Friedrich de Wolf, MD^{1,2}

Carsten Willem Arnoldussen, MD³

Jochen Grommes, MD⁴

Shu Gi Hsien, MD¹

Patricia Joan Nelemans, MD, PhD⁵

Michiel Willem de Haan, MD, PhD³

Rick de Graaf, MD, PhD³

Cees Hendrikus Wittens, MD, PhD^{1,4}

¹ Department of Surgery, Maastricht University Medical Centre, Maastricht

² School for Cardiovascular Diseases (CARIM), Maastricht University Medical Centre, Maastricht ³Department of Radiology, Maastricht University Medical Centre, Maastricht

⁴ Department of Vascular Surgery, Aachen University Hospital, Aachen, Germany

⁵ Department of Epidemiology, Maastricht University Medical Centre, Maastricht

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ABSTRACT

Background

As one of the primary etiologies of the post-thrombotic syndrome, chronic venous occlusion is a huge burden on patient quality of life and medical costs. In this study, we evaluate the short-term and midterm results of endovenous recanalization by angioplasty and stenting in chronic iliofemoral deep venous occlusions.

Methods

This is a retrospective observational study set in a tertiary medical referral center. Patients with venous claudication or C4-6 venous disease combined with duplex and magnetic resonance-confirmed iliofemoral or caval occlusion were included. Patients with recent deep vein thrombosis (<1 year) were excluded. The intervention was endovascular deep venous recanalization, followed by angioplasty and stenting. Safety and feasibility were clinically evaluated during the procedure and during follow-up. Reocclusions and other treatment failures were evaluated during a maximum follow-up of 31 months by ultrasound imaging and venography.

Results

Seventy-five procedures were performed in 63 patients (average age, 44 years; range, 18-75 years), of whom 86% had a history of deep venous thrombosis. The mean time between the initial deep venous thrombosis and treatment with PTA and stenting was 12 years (maximum, 31 years). May-Thurner syndrome was present in 57%. Forty-two procedures were performed in the left, six in the right, and 11 in both lower extremities. The vena cava inferior was partially stented in 25 patients. An average of 2.6 stents (median, 2) were used per procedure. Primary patency was 74% after 1 year. Assisted primary and secondary patency rates were 81% and 96%, respectively, at 1 year. Secondary procedures included restenting, catheter-directed thrombolysis, endophlebectomy of the common femoral vein, and creation of an arteriovenous fistula. No clinically evident pulmonary emboli were noted. A bleeding complication occurred after six procedures and was deemed major in two. No patients died. Relief or significant improvement of symptoms of chronic venous occlusive disease was achieved in 81% of patients.

Conclusions

Endovenous recanalization by angioplasty and stenting of chronically occluded iliofemoral vein segments is a safe and effective treatment with good short-term results, even when treatment takes place decades after the initial deep venous thrombosis. Most reocclusions can be adequately treated by a secondary procedure.

INTRODUCTION

Iliofemoral occlusions are a prevalent cause of chronic venous pathology.^{1,2} Besides or in combination with chronic deep venous insufficiency, venous occlusive disease is the primary cause of development of venous hypertension and the post-thrombotic syndrome (PTS).^{2,3} The symptoms associated with occlusion of the deep venous system of the lower extremity range from relatively mild complaints (ie, itching and small superficial varicosities) to venous claudication and venous ulcers. Therefore, iliofemoral occlusions causing PTS are a major cause of morbidity and reduced quality of life (QOL) in Western societies.⁴⁻⁷ Deep venous thrombosis (DVT) and PTS are also a huge burden on direct health care-related costs as well as indirect costs due to work absenteeism.^{6,8,9}

In the acute phase of a DVT, the thrombus creates an occlusion of the vein lumen. At that moment, venous outflow is only possible through collateral veins. This is especially problematic in the iliofemoral veins because no functionally effective collateral network is present.¹⁰ Owing to only limited recanalization after acute iliofemoral DVT, the long-term restriction of venous outflow develops.¹ The natural ability of the vein to adjust its diameter, depending on the amount of venous outflow of the leg, is also restricted, possibly leading to venous claudication during exercise. Furthermore, ipsilateral DVT recurrence, which is frequent in these patients, worsens outcome even more.¹¹⁻¹⁷ External compression of a vein is the second most prevalent cause of deep venous obstruction and also an important risk factor for DVT.^{18,19} May-Thurner syndrome is the most frequently occurring type of external compression and is a frequently missed diagnosis in the DVT population and also in the general asymptomatic population.¹⁸⁻²⁰

The current standard DVT treatment consists of elastic compression stockings, anticoagulation with low-molecular-weight heparin, followed by oral anticoagulation with vitamin K antagonists, and mobilization. Treatment is primarily aimed at preventing pulmonary embolism and reducing thrombus propagation.²¹ However, this treatment in most patients can only realize a limited thrombus lysis, especially in cases of iliofemoral DVT.^{22,23} The effectiveness in preventing long-term occlusion is therefore modest. Treatment of PTS is currently mostly based on compression therapy, a suboptimal treatment that has low patient compliance.^{3,4,21,24} None of these therapy options prevent the development of venous hypertension, and therefore, the complaints and symptoms of patients are not targeted directly. Percutaneous transluminal angioplasty (PTA) and stenting have been used in the arterial system for decades, and their use in the venous system has been pioneered since the late 1990s. Recent work in specialized centers has shown favorable results of these treatments, but their use is still far from accepted as standard patient care.^{23,25-28}

The aim of this study was to evaluate the early results of PTA and stenting in patients

with extensive chronic, mostly post-thrombotic, venous occlusions, treated at a national referral center.

Methods

In this observational study, we retrospectively included patients treated between January 1, 2009, and February 1, 2012. The study included patients with chronic complaints of severe venous symptoms (CEAP scores C4-6) or venous claudication combined with signs of deep venous occlusion confirmed by magnetic resonance venography (MRV) or duplex ultrasound (DUS) imaging. Patients presenting with recent DVT (<1 year) or who received catheter-directed thrombolysis before stenting were excluded. Testing for hypercoagulable factors was performed in all PTS patients not currently being treated with oral anticoagulants.

Diagnostic workup

Patients with suspected chronic iliac vein obstruction were analyzed with DUS imaging and MRV. The scanning protocols and equipment have been described previously.^{10,29} When a chronic iliac vein obstruction was suspected, we specifically looked for the location and extent of obstruction to plan our interventional approach. We also evaluated the patency of the common femoral vein, identified the presence of collateral pathways or external compression, or both, and the outflow through the inferior vena cava. Evident external compression of the left common iliac vein with clear diameter reduction on MRV and DUS was considered a May-Thurner syndrome in patients with accompanying clinical signs.

MRV assessment

MRV examinations were performed on a 1.5-T Intera MRI system (Philips Medical Systems, Best, The Netherlands). For signal reception, a dedicated 12-element phased-array peripheral vascular coil with craniocaudal coverage of 128 cm (Philips Medical Systems) was used. Patients were placed supine for imaging. A fixed dose of 10-mL gadofosveset trisodium (Ablavar; Lantheus Medical Imaging, Billerica, Mass), a blood pool contrast agent, was administered intravenously as a single dose at a speed of 1.0 mL/s in the median cubital vein, using a remote-controlled injection system (Medrad Spectris, Indianola, Pa). A five-station three-dimensional ultrafast gradient echo sequence with fat suppression (spectral presaturation with inversion recovery) was used for high-resolution steady-state imaging of the venous vasculature, ensuring a coverage of at least the popliteal veins up to the entire IVC. Acquisition parameters were repetition time, 7.8 ms; echo time, 3.8 ms; field of view, 380 mm; matrix, 400; 150 axial slices per station, and voxel dimensions (reconstructed) were 0.95 0.95 1.50 mm for all stations.

DUS imaging

DUS examinations were performed using a Hitachi Aloka ProSound ALPHA 7 Premier machine (Aloka, Tokyo, Japan). A convex array transducer, UST-9130 (frequency range,

3-6 MHz), was used when studying the venous system from the vena cava down toward the tibial veins below the knee, with the patient supine. Consequently, all patients were also examined standing, with scanning from the upper groin to below the knee using a high-frequency UST-54II (frequency range, 5-16 MHz) compound linear array transducer, with pulsed-wave Doppler (5 MHz) used to test for valvular incompetence. Optimal distal vena cava and common iliac vein diameter distension were analyzed during enhanced flow with vertical leg extension when the patient was supine.

Recanalization, PTA, and stenting.

Depending on the findings during the diagnostic workup, as described above, the procedure took place in a dedicated intervention room at the radiology department or in a dedicated vascular surgical suite with fluoroscopic assistance, allowing for a combined approach of endophlebectomy of the common femoral vein, with or without an arteriovenous fistula (AVF), and recanalizing the iliac obstruction. Procedures were performed under general anesthesia and local infiltration analgesia. Cannulation of the popliteal vein (with the patient prone) or femoral vein (midthigh, with the patient supine) was performed under ultrasound guidance (CX50 CompactXtreme; Philips). After cannulation, a 5F sheath (AVANTI; Cordis Corp, Syracuse, NY) was introduced, and an antegrade venogram was performed. After assessing the presence, location, and extent of an obstruction, the interventional radiologist navigated to and through the obstruction with the use of various stiff guidewires (Terumo Medical Corp, Somerset, NJ) and catheters. Crossing the obstructed segments could be challenging, but with the anatomic information from the preprocedural MRV combined with 2D and 3D angiography images acquired during the procedure, we were able to identify the correct pathway and cross the obstruction in all but three patients. Understanding 2D and 3D MRI and angiographic anatomy combined with choosing the most suitable catheter and guidewire is crucial. Depending on the location of the obstruction, predilatation was performed with balloon catheters sized 8 to 12 mm 40 mm (Powerflex; Cordis Corp) or 14 40 mm (Foxcross, Abbott Laboratories, Abbott Park, Ill). After dilation, one or more self-expandable stents, sized from 14 60 to 100 mm up to 26 80 mm, including Sinus-XL (Optimed, Ettlingen, Germany), Wallstent (Boston Scientific, Natick, Mass), Zilver Vena (Cook Corp), and Andrastent XL (Bioassist, Albuquerque, NM), were deployed at the predilated site. Stent sizing was determined by location and vessel diameter proximal and distal to the occlusion, aiming at 20% oversizing to ensure anchoring to the vein wall. After stent placement, the stented trajectory was dilated with a semicompliant Coda balloon (Cook Corp), further anchoring the stents to the wall. Venograms above, below, and at the level of the obstruction were repeated to assess the results. At the end of the procedure, the sheath was removed, and local pressure was applied until hemostasis was achieved (Figures 1 and 2 show preprocedural venography examinations in a case of successful PTA and stenting, Figure 3 shows the control radiograph examination after stent placement, and Figure 4 shows the final control venography).

Figure 1. Venography of the left common iliac vein shows an occlusion of the common iliac vein, and multiple collateral veins are visible.

Figure 2. Venography of the trajectory of the inferior vena cava shows occlusion of the inferior vena cava with prominent collaterals along the lumbar spine.

During a number of procedures, an endophlebectomy (ie, surgical desobstruction) was performed in which the post-thrombotic vein was longitudinally opened, intraluminal scar tissue was carefully removed, and the venotomy was closed without use of a patch. This was done in patients in whom perioperative inflow into the stent was deemed insufficient and was accompanied in a limited number of patients by the creation of an AVF between the femoral vein and femoral artery to ensure a further improved inflow in the stented tract. Inflow can be expected to be insufficient when extensive post-thrombotic aberrations are present in the common femoral vein, because these cannot be adequately treated with PTA alone, and stenting beyond the inguinal ligament has shown unfavorable results. A clear relation between venographically determined poor flow from the profunda femoral vein into the common femoral vein and a reduced flow through the stent was also shown.

Postoperatively, regardless of preoperative anticoagulation, patients were anticoagulated with a regimen of subcutaneous low-molecular-weight heparin for a minimum of 5 days.

During this period, patients started treatment with oral anticoagulants (acenocoumarol or phenprocoumon) for a minimum of 6 months, with a target international normalized ratio of 2.5 to 3.5. DUS imaging was performed the day after the procedure to assess the venous outflow and stent patency. Patients were usually discharged #48 hours. Standardized follow-up was planned for each patient at 6 weeks, 3 months, 6 months, and 1 year. At these visits, clinical symptoms and complaints were assessed as well as patency on DUS (Venous Clinical Severity Score or QOL scoring were not possible because of the retrospective character of this study).

Figure 3. Radiograph of the abdomen after recanalization and stent placement shows multiple stents placed in the inferior vena cava and iliac veins on the left and right side.(left)

Figure 4. Final control venography shows adequate outflow toward the heart in the recanalized and stented inferior vena cava and iliac veins. The collateral pathways are no longer visible, confirming the patency of the newly created iliac-caval outflow pathway.(right)

Statistical analysis

Categoric data are presented as frequencies and percentages, and continuous data are presented as mean values $\pm$ the standard deviation or median values with the range, unless otherwise stated. Categoric data were analyzed by χ^2 test. Cumulative probabilities of patency at 3, 6, and 12 months after initial treatment were calculated using Kaplan-Meier survival analysis. For the evaluation of primary patency, the need for additional treatment by an assisted primary intervention or a secondary intervention, or obstruction, at the end of follow-up was considered a treatment failure. For the evaluation of secondary patency, only obstruction at the end of follow-up was considered a treatment failure. Follow-up time was defined as the period between initial treatment and treatment failure or the period between initial treatment and date of the last observation (in patients without treatment failure). Data were analyzed with SPSS 17.0.1 (SPSS, Chicago, Ill) and Stata 11.2 (StataCorp. Collage Station, Tex) software. Values of $P \leq .05$ were considered to indicate statistical significance.

RESULTS

Demographics. During the study period, 63 patients (45 women [71%]) with chronic deep vein obstructions were treated in our center (Table 5 summarizes demographic data). Patients had a mean age of 44 ± 12.4 years (range, 18-75 years). The obstruction in 54 patients (86%) was secondary to a DVT in the patient's medical history, and 17 (27%) had a history of recurrent DVT. Imaging showed a total occlusion in 39 patients (62%), subtotal occlusion in 15 (24%), and May-Thurner syndrome without a history of DVT in nine (14%). The interval between the DVT event (the first in those with recurrent DVT) and PTA and stenting was 11.9 ± 9.3 years (median, 9; range, 1-31 years). The DVT (if present in patient history) was located on the left side in 37 (69%), on the right in five (9%), and was bilateral in 12 (22%). May-Thurner syndrome was present in 36 patients (57%) and was present in 62% of women vs 28% of men; however, this did not reach statistical significance ($p=.09$).

Table 5. Demographic information of the study population

Variable	No. (%)
Patients, No.	63
Procedures, No.	75
Male/female sex	1:2.5
Mean age, years (range)	44 (18-75)
Primary vs secondary etiology	1:6
Deep vein thrombosis	
Left side	37 (68.5)
Right side	5 (9.3)
Bilateral	12 (22.2)
May-Thurner syndrome	36 (57.1)
Thrombophilia present	11 (52.4) ^a

^aThrombophilia testing was only possible in 21 patients not taking oral

A thrombophilic disorder was found in 11 of 21 tested patients (52%), comprising 33%

of the total population. Most patients could not be tested for thrombophilia before or during follow-up because of ongoing anticoagulation treatment. A factor V Leiden mutation was found in seven patients, factor II mutation in two, an antithrombin 3 deficiency in one, and a protein S and C deficiency in one. The median CEAP classification C score was 3 (mean, 3.3) at presentation (Table 6).³⁰ Thirty-five patients (56%) were scored as C1-3, and therefore were treated because of their venous claudication.

Table 6. Preprocedural CEAP clinical CLASS³⁰

CEAP C	No.	(%)
C1	8	12.7
C2	13	20.6
C3	14	22.2
C4	14	22.2
C5	8	12.7
C6	6	9.5

Procedures

A total of 75 procedures were performed in 63 legs; of these, 55 (73%) were performed on the left venous tract, six (8%) on the right side, 11 (15%) bilaterally, and in three patients (4%), only the vena cava was treated. A median of two stents (mean, 2.6 6 1.6) was used per procedure; the distribution of stent numbers used is reported in Table 7.

During eight procedures (11%), an endophlebectomy of the common femoral vein was performed to secure sufficient inflow of the stented vein segments; during four of these procedures (5%), inflow into the femoral confluence seemed insufficient (according to the operative visual evaluation), and an AVF was created to guarantee adequate inflow. An immediate reocclusion in the stent was noted on the final control venography after three procedures (4%), and these were adequately treated with direct rePTA and expansion of the stented segment in two patients, and in one patient, delayed surgical thrombectomy and creation of an AVF was performed. All three were patent at last follow-up. Moreover, the control DUS the day after eight stenting procedures (11%) showed the stented segments were rethrombosed. These were treated with initial catheter-directed thrombolysis in six patients (10%), secondary PTA and stenting was performed in five (8%), four (6%) were treated with surgical thrombectomy, and an AVF was created in five (8%).

Table 7. Number of stents used per procedure

Stents used	No. (%)
1	(32.4)
2	(24.3)
3	(21.6)
4	(10.8)
5	(2.7)
6	(4.1)
7	(4.1)

Other procedure-related complications included six (10%) bleeding-related complications (four nonsevere postprocedure hemorrhages at the puncture site treated by manual compression, one infected hematoma developed necessitating open surgery, and one common femoral artery was punctured during sheath introduction), a heparin-induced thrombocytopenia developed in one patient, and superficial wound

problems occurred in two patients after surgical desobstruction. No clinically evident pulmonary emboli, no stent migration, and no procedure-related or unrelated deaths were documented.

Follow-up

Mean follow-up duration was 8.8 $\pm$ 8.0 months (range, 1-31 months). Follow-up data >6 months and 1 year are present for 36 (57%) and 19 patients (30%), respectively. Primary patency was 88% after 3 months, 83% after 6 months, and 74% after 12 months. Assisted primary patency rates were 89%, 87%, and 81%, and secondary patency rates were 96%, 96%, and 96% after 3, 6, and 12 months, respectively (Figure 5; Table 8).

Figure 5. Kaplan-Meier curves show primary, assisted primary, and secondary patency rates. Numbers at risk and lost patency are provided below the graph.

After seven procedures (9%), rethrombosis of the stented vein segment occurred after discharge from the hospital. After 15 procedures (20%), stenosis of the stented vein tract was observed and was deemed clinically and hemodynamically (on DUS) significant in three patients (4%). Because of reocclusion and stenosis, restenting was performed after eight primary procedures, thrombolysis was performed in seven, an endophlebectomy of the femoral tract was performed in two (during follow-up), and creation of an AVF was performed once during follow-up. Moreover, restenting was performed after two cases of stent kinking, after one stent fracture, and in two patients with chronic stent-related pain. In short, 23 reinterventions were performed in 13 patients (21%).

Table 8. Kaplan-Meier estimates of primary, assisted primary, and secondary patency rates

Variable	3 months	6 months	12 months
<u>Primary patency</u>			
Rate (95% CI)	87.6 (75.6-93.9)	82.7 (69.0-90.7)	74.3 (58.5-84.9)
Standard error	0.044	0.053	0.067
Lost to follow-up, No.	15	7	8
<u>Assisted primary patency</u>			
Rate (95% CI)	89.3 (77.6-95.1)	87.0 (74.3-93.6)	81.4 (66.7-90.1)
Standard error	0.042	0.047	0.058
Lost to follow-up, No.	15	7	8
<u>Secondary patency</u>			
Rate (95% CI)	96.1 (85.1-99.0)	96.1 (85.1-99.0)	96.1 (85.1-99.0)
Standard error	0.027	0.027	0.027
Lost to follow-up, No.	16	7	11

CI, Confidence interval

Total relief of symptoms and complaints occurred in 35 patients (60%), partial improvement in symptoms and complaints occurred in 12 (21%), and no improvement was achieved in 11 patients (19%); follow-up data for this were not available for five patients. Relief of symptoms was seen in 86% of patients not suffering a rethrombosis and in 75% of patients in whom a reocclusion occurred, but this did not reach statistical significance ($p=.34$).

DISCUSSION

This study shows favorable short-term technical success rates, reasonable primary and assisted primary midterm patency rates, and excellent secondary patency rates of chronically occluded iliofemoral tract, with and without caval involvement, treated with endovascular PTA and stent placement. Similar results have been presented in other recent studies.^{22,24-27} Our study and experience show reocclusion to occur in less than one-fourth of patients. Furthermore, in those with reocclusions, the clinical outcome after the acute reocclusion event did not worsen compared with clinical symptoms and complaints before stenting. Also notable is that in the subgroup of 15 patients who developed a reocclusion of the treated vein segment, eight still showed clear clinical improvement, and in four of these patients, any restenting was therefore postponed until clinical signs returned because the treatment window for thrombolysis had passed. The mechanism behind this phenomenon is unclear. Possibly the acute

occlusion of a rethrombosis ameliorates any previously present venous insufficiency. Most important, our results show that it is possible to safely and effectively treat post-thrombotic lesions decades after the initial DVT in patients with severe venous disease (C4-6 or venous claudication, or both), where previously life-long compression therapy was the only treatment option.

Because we only started using the techniques described in this study in 2009, all patients with chronic deep venous occlusion treated in our hospital were included in this study. Therefore, those patients treated during what one might call our “learning curve” have also been included. This is reflected in the relative high number of early reocclusions (after eight procedures), of which all but one occurred in the first year we performed PTA and stenting. These procedures were generally not performed in a hybrid manner. In cases of insufficient flow, it was therefore not possible for the dedicated venous surgeon to perform an endophlebectomy or creation of an AVF during the primary procedure. Secondary interventions were therefore postponed. These issues have since been addressed, and immediate interventions were possible in all following patients. This, however, underlines the importance of performing these types of treatment in dedicated centers.

Stenting in patients with May-Thurner syndrome showed a statistically nonsignificant lower risk of rethrombosis compared with the subpopulation without the syndrome (reocclusion of 20% in those with vs 33% in those without May-Thurner syndrome; $P = .124$), possibly because of more elaborate post-thrombotic aberrations in those without May-Thurner syndrome. Known presence of thrombophilia showed no clear effect on chance of reocclusion. However testing for thrombophilia was not possible in most patients because they were treated with oral anticoagulants at the time of inclusion and follow-up. Poor stent inflow at the end of the procedure has been identified as an important risk factor for reocclusion in our experience. We therefore increasingly perform an endophlebectomy of the femoral tract to guarantee adequate stent inflow.

Compared with other recently published studies, a relative low number of non-post-thrombotic patients are included in our study, undoubtedly because of patient selection by physicians referring to our tertiary clinic. Therefore, the number of patients with extensive post-DVT defects was high, and the delay in treatment was very long in many patients. Moreover, because of logistic reasons in The Netherlands, most patients with acute extraluminal compression of deep veins caused by cancer are not referred to our center. We therefore tend to mostly treat long-term sequelae of DVT, which tend to be the most technically complex and clinically complicated cases.

Because nearly all of our patients received at least one Sinus XL stent, we cannot differentiate for outcome between the different stents used. However, we believe from the results of radiographs and venography examinations that many cases of

rethrombosis and stenosis can be attributed to poor stent adaption to the forces within the venous system. Rigidity and low radial force especially seem to precede stent-related complications. New dedi-cated venous stents, characterized by high flexibility and high radial force, will be commercially available in the near future and should address these problems effectively. We also find it noteworthy that five patients underwent restenting because of stent-related problems (kinking or fracture of the stent and stent-related chronic pain), without any sign of reocclusion. Re-evaluating the need for stent anchoring in the caval vein, use of anticoagulation, and the method of stent alignment when using these new stents is very important because these might affect patient outcome and will warrant future research.

CONCLUSIONS

Endovascular recanalization with PTA and stent placement of chronically occluded iliofemoral deep venous tracts is an effective treatment option with good short-term clinical and hemodynamic results, even decades after the initial DVT. Early reocclusion occurred relatively frequent in this series; however, improving logistics addressed this adequately. Secondary patency can be achieved and maintained in nearly all patients.

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CHAPTER 4

SHORT-TERM CLINICAL EXPERIENCE WITH A DEDICATED VENOUS NITINOL STENT: INITIAL RESULTS WITH THE SINUS-VENOUS STENT

M.A.F. de Wolf¹

R. de Graaf²

R.L.M. Kurstjens¹

S. Penninx¹

H. Jalaie³

C.H.A. Wittens^{1,3}

¹ Department of Vascular Surgery and Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands

² Department of Radiology, Maastricht University Medical Centre, Maastricht, The Netherlands

³ Department of Vascular Surgery, University Hospital RWTH Aachen, Aachen, Germany

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ABSTRACT

Objective

Deep venous stenting has become the primary treatment option for chronic venous obstructive disease, both for iliac vein compression and post-thrombotic venous lesions. Until recently, only stents aimed at arterial pathology were used, because no dedicated venous stents were available. However, three such stents have now become available. These venous stents are characterized by increased length, diameter, flexibility, and radial force. This study reports an early experience with one of these devices; the sinus Venous stent (OptiMed GmbH, Ettlingen, Germany).

Methods

Between March 2012 and July 2014, 75 patients were treated with the sinus Venous stent: 35 cases of iliac vein compression syndrome and 40 cases of unilateral chronic obstruction in post-thrombotic syndrome (PTS). Diagnosis of relevant obstruction was made using clinical evaluation, duplex ultrasound, and magnetic resonance venography. Patency during follow up was assessed with duplex ultrasound. Clinical improvement was assessed by VCSS, Villalta score, rate of ulcer healing, and improvement of venous claudication.

Results

The cumulative patency rates at 3, 6, and 12 months were 99%, 96%, and 92%, respectively. The cumulative assisted primary patency rates were 99% at 3, 6, and 12 months. The cumulative secondary patency rate at 12 months was 100%. Differences exist in patency rate between the subgroups of non-thrombotic and post-thrombotic, with the first showing no reocclusions. All rethromboses in the PTS group were treated by ancillary treatment modalities. VCSS and Villalta score decreased significantly after stenting, as did venous claudication. Morbidity was low without clinically relevant pulmonary embolism, and mortality was nil. Although two out of seven ulcers healed temporarily, no ulcer remained healed at 12 months follow up.

Conclusion

Short-term clinical results using the sinus Venous stent are excellent, with significant symptom reduction, low morbidity rates, and no mortality. Loss of stent patency is seen less often compared with arterial stents described in the literatures.

INTRODUCTION

Therapy for chronic deep venous disease has long been characterized by the sole use of conservative treatment modalities, both in cases of valvular insufficiency and venous obstructive disease. Open surgical or endovascular approaches were reserved for the most severe cases, which still holds true for deep venous valvular insufficiency. In recent years, however, the treatment options in chronic deep venous obstructive disease have changed dramatically. Endovascular treatment, by use of percutaneous transluminal angioplasty (PTA) and stenting of post-thrombotic obstructions and venous compression syndromes, such as May-Thurner syndrome (MTS), has become standard care in a large number of specialized centers worldwide. The low morbidity, absence of mortality, and excellent short and long-term results mean that worldwide interest in this type of treatment is rapidly increasing and more and more centers are starting to offer this treatment. It is, therefore, remarkable that until very recently no stents dedicated to deep venous pathology were available.

Neglén et al. showed good results with the Wallstent, a metal stent frequently used in arterial pathology, with high radial force, although limited flexibility and poor positioning qualities.¹ Also, nitinol stents have been used and show comparable results between study groups.² Recent study of arterial designed self-expanding nitinol stents in a mostly post-thrombotic population, showed patency rates of 74%, 81%, and 96% at 1 year for primary, assisted primary, and secondary patency, respectively.³ The arterial design, however, incorporates properties that might hamper applicability in the venous system.⁴ Arterial and venous anatomy and hemodynamics differ greatly in physiological and pathophysiological conditions; especially in terms of shear stress, vessel diameter, and flexibility. Moreover, PTA and stenting in arterial disease is generally reserved for pathology of atherothrombotic origin, without scarring of the vessel wall and or external compression.

Recently a number of dedicated venous stents have been announced or became available; namely the Veniti Vici (VENITI inc., St. Louis, MO, USA), Zilver Vena (Cook, Bloomington, IN, USA), and sinus Venous (OptiMed, Ettlingen, Germany). All three devices are designed to accommodate the need for greater length, diameter, flexibility, and radial force in the venous system. To the authors' knowledge, only clinical data regarding the Zilver Vena have been published. O'Sullivan et al. showed excellent results for the Zilver Vena stent in a challenging population with many acute DVT patients and malignant venous obstructions; they reported a short-term patency rate of 85%.⁵

This study evaluates safety and short-term clinical outcome when using the sinus Venous stent in routine patient care at a tertiary venous center. As iliac vein compression syndromes differ greatly in their etiology from post-thrombotic disease, use of the

device will be evaluated separately for both types of pathology.

METHODS

The study included 75 patients treated for symptoms and complaints related to unilateral chronic iliofemoral venous obstructive disease with the sinus Venous stent at a tertiary referral hospital, between March 2012 and July 2014. Patients who were suspected of having iliofemoral deep venous obstruction received both duplex ultrasonography (DUS) imaging and magnetic resonance venography (MRV) to confirm the diagnosis.⁶ Patients were included when: (A) signs of unilateral iliofemoral deep venous obstruction were present on DUS and MRV (>50% diameter stenosis and the presence of a collateral network), (B) clinically significant signs and symptoms of chronic obstructive venous disease were present, and (C) the femoral and deep femoral veins were patent. Patients with inferior vena cava involvement or bilateral iliofemoral occlusive disease were excluded. Furthermore, patients were excluded in whom post-thrombotic aberrations extended below the level of the saphenofemoral junction in the common femoral vein, as these patients are treated in a hybrid fashion, stent placement combined with endophlebectomy and AV fistula creation.⁷ Moreover, patients with a history of DVT less than 1 year ago were excluded as sufficient natural recanalization might still occur.⁸ Upon intake baseline data were collected, consisting of CEAP, Venous Clinical Severity Score (VCSS), Villalta score, and assessment of venous claudication.^{9e11} Venous claudication was defined as the onset or worsening of pain and/or heaviness during (mild) exercise, which subsides during rest, especially when sitting or lying down. Venous claudication was only considered in patients with a proven venous obstruction. The location and extent of obstruction or external compression, the presence of collateral veins, the inflow at the common femoral vein from all three major branches (great saphenous vein, femoral vein and deep femoral vein), the outflow through the inferior vena cava and valve competence (< 0.5 seconds of reflux) all were evaluated. Left iliac vein compression (LIVC) or right iliac vein compression syndrome was considered when external compression of the common iliac vein (CIV) created >50% diameter reduction at this point as shown by DUS and/or MRV and collaterals were present.^{12,13}

Duplex ultrasonography

DUS examination was done using a Hitachi Aloka ProSound ALPHA 7 Premier machine (Aloka, Tokyo, Japan) and consisted of scanning the venous system from the suprarenal vena cava down to the common femoral vein in the supine position with a convex array transducer, UST-9130 (frequency range, 3e6 MHz). Using a high-frequency UST-5411 (frequency range, 5e16 MHz) compound linear array transducer with pulsed wave Doppler (5 MHz), scanning from the upper groin to below the knee to test for distal obstructive lesions (>50% diameter reduction) and valvular incompetence (>0.5s

reflux), in the standing position, was performed.

Magnetic resonance venography

All MRV examinations were performed on a 1.5-T MRI system (Achieva, Philips Medical Systems, Best, the Netherlands). The technique has been described in detail before.⁶ In short, a dedicated 12 element phased array peripheral vascular coil with a craniocaudal coverage of 128 cm (Philips Medical Systems) was used for signal reception. A fixed dose of 20 mL gadobutrol (Gadovist 1.0, Bayer Schering Pharma, Berlin, Germany) was administered intravenously as a single dose at a rate of 1.0 mL/s in the median cubital vein, using a remote controlled injection system (Medrad Spectris, Indianola, PA, USA). A five station three dimensional ultrafast gradient echo (TFE) sequence with fat suppression (SPIR) was used for high resolution imaging of the venous vasculature from the popliteal veins up to the right atrium.

PTA and stenting

Procedures were performed in a dedicated angiosuite (AlluraClarity, Philips Medical Systems, Eindhoven, the Netherlands). All interventions in post-thrombotic syndrome (PTS) patients were performed under general anesthesia, while iliac vein compressions were treated under local anesthesia. Heparin (5,000 IU) was administered to all patients currently not using oral anticoagulants, and coumadin was continued in all other cases (a maximum INR of 4 was accepted at the time of intervention). Venous access was obtained through the ipsilateral femoral vein, at least 15 cm distal to the femoral confluence under ultrasound guidance. A 10F sheath was needed to facilitate stent introduction. The technique for traversing stenotic and occluded venous segments has been described before.¹⁴ Predilatation to the size of the anticipated stent is essential for sinus Venous stents. Predilatation was done increasing in size from 12 to 16 mm from the common femoral vein to the common iliac vein (12 mm powerflex and 16 mm maxi LD, Cordis, Johnson & Johnson, Diegem, Belgium; 14 mm Armada, Abbott, North Chicago, IL, USA). Maximum pressure needed for full balloon expansion was 12 atm. All venous segments were stented with the sinus Venous. Postdilatation was always performed. Poststenting assessment of in and outflow was done by single plane anteroposterior angiography. Conebeam CT imaging was performed to evaluate stent configuration and apposition. Post intervention, patients were generally discharged the next day. The anticoagulation regimen consisted of 6 months of treatment with coumadin, with a target INR of 3e4, according to Dutch guidelines for thrombosis service.¹⁵ This regimen was started the evening after the intervention. Full dose tinzaparine was started directly post-intervention and continued until the INR was >3 on two separate days. Antiplatelets were not used. In patients already using coumadin prior to the intervention, these drugs were continued during hospitalization.

Follow-up

Standardized follow up was performed at 2 and 6 weeks and 3, 6, and 12 months post

intervention. Follow up data collection consisted of VCSS and Villalta score assessment, rate of relief of venous claudication and ulcer healing (defined as full reepithelialization). DUS was performed to assess patency at every visit. Patency was defined as flow in a lumen with <50% diameter compared with the stent diameter. All data were collected prospectively using a preset protocol.

Statistical analysis

Frequencies and percentages were used to present categorical data. Median values with the range were used for continuous data. Categorical data were analyzed by the χ^2 test. Kaplan-Meier survival analysis was used to calculate patency rates. An α of .05 was used to indicate statistical significance.

Ethical approval for research

Under Dutch law, patients treated at a university hospital give automatic consent for their anonymized data to be used in research, unless explicit objections are made.

RESULTS

Demographics

Seventy-five patients with unilateral chronic iliofemoral venous obstruction (CVO) were treated by placement of the sinus Venous stent during the study period. The median age was 45 years (range 18–77), and 49 (65%) patients were female. Complaints and symptoms were caused by post-thrombotic disease in 40 (53%) patients. In the other 35 (47%) patients, CVO was caused by primary iliac vein compression syndrome (left sided in 33 patients). In the post-thrombotic patient group, 35 (88%) had suffered a DVT in their medical history. In the other five patients no DVT was ever diagnosed clinically; however, there were signs on MRV and DUS of vein wall scarification and trabeculation in the common and/or external iliac vein, consistent with prior DVT (Table 9). All post-thrombotic iliofemoral obstructive lesions were occlusive on the intraprocedural venogram. Post-thrombotic occlusion was restricted to the CIV in two (5%) patients, present in CIV and external iliac vein (EIV) in five (13%), present in the EIV and common femoral vein (CFV) above the saphenofemoral confluence in four (10%) and extending from the CIV to the CFV above the saphenofemoral confluence in 29 (73%) patients. C class of CEAP was C4e6 (i.e. skin changes) in 21 (28%) patients. Forty (53%) patients presented with venous claudication. Based on the Villalta scale, 13 (33%) legs were scored as having mild, 11 (28%) moderate, and 13 (33%) severe PTS. In three (8%) patients the Villalta scale was <5 points, that is venous claudication was the indication for treatment in those patients (which highlights the inability of the Villalta scale to adequately assess PTS in some cases). Venous claudication was present in 25 (63%) patients in the PTS and 16 (46%) in the iliac vein compression groups. Seven (9%) patients had an active venous ulcer, four in the PTS, and three in the iliac vein

compression syndrome group. Other demographics and subdivision into subgroups can be found in Table 9.

Table 9. Demographics of the total, PTS, and iliac vein compression subgroups

	Baseline	Total	PTS	IVCS
N	75		40	35
Number of females	49	65%	24	53%
Average age (years)	45	(17-77)	45	(17-68)
Single DVT	38	51%	28	70%
Recurrent DVT	9	12%	7	18%
Silent DVT ^a	5	7%	5	13%
Time between DVT and treatment (years)	6	(1-37)	6	(1-37)
Left sided DVT			29	83%
Right sided DVT			5	14%
Bilateral DVT			1	3%
Left sided stenting	72	96%	39	98%
Right sided stenting	8	11%	6	15%
C-class 0	8	11%	4	10%
C-class 1	9	12%	7	18%
C-class 2	13	17%	6	15%
C-class 3	24	32%	11	28%
C-class 4	11	15%	6	15%
C-class 5	3	4%	2	5%
C-class 6	7	9%	4	10%
Median Villalta			11.5	(2-24)
Venous claudication	40	53%	25	63%
Superficial venous reflux	61	81%	33	83%
Deep venous reflux	19	25%	12	30%
Perforator vein reflux	17	23%	5	13%

^a Silent DVT: no anamnestic history of DVT, but clear signs of previous DVT on imaging.

Procedure

All post-thrombotic occlusions required recanalization. Technical success was achieved in all cases. In 43 patients (57%) one stent was used, in 27 patients (36%) two stents, and in five patients (7%) three stents were used. When applicable, the stent was placed as accurately as possible at the iliac confluence to cover the obstruction, with special care not to cover the contralateral inflow.

In three patients, however, one in the PTS group and two in the iliac vein compression group, positioning was deemed too central into the inferior vena cava (IVC), touching the IVC wall and thereby covering the contralateral inflow. No further action was taken. In a fourth patient acute thrombosis of the stented tract was observed during the

procedure and was directly and successfully treated by percutaneous thrombectomy. Throughout follow up this patient's stents remained patent. Intraprocedural kinking and/or fracture of stents were not seen.

Follow-up

The ultrasound examination at 2 weeks showed suboptimal positioning of the CIV stent in two patients with iliac vein compression lesions. In both cases, the stents were placed too peripherally, resulting in persistent compression of the left CIV by the overlying right common iliac artery (which did not require restenting as the recurrent stenosis was <50%). Optimal stent distention was seen in all cases distal to the CIV. Mild compression, that is oval rather than round configuration of the stent was noticed at the level of the left common iliac vein because of the overriding right iliac artery in most cases (Figure 6); however, no significant diameter stenosis (>50%) was seen, compared with the diameter of a fully expanded stent.

Figure 6. Ultrasound control after stenting the common iliac vein on the left side to treat May-Thurner syndrome, showing the typical oval shape of the stent with sufficient radial force to lift the overlying right common iliac artery. Smallest intraluminal diameter is 7.6 mm, compared with 12 mm more distally, but with a very adequate surface area of 1.23 cm².

Patient follow up had a median duration of 5.4 (range 1.018.0) months. The overall cumulative primary patency was 99% at 3 months, 96% at 6 months, and 92% at 12 months. Assisted primary patency rates were 99% at 3, 6 and 12 months, and the secondary patency rate was 100% during the total follow up period (Figure 7A). Cumulative primary patency rates for the iliac vein compression group were 100% during follow up (Figure 7B). The cumulative primary patency rates of the post-thrombotic group at 3, 6, and 12 months were 97%, 93%, and 85%, respectively (Figure 7C). For all reported patency rates the standard error of the mean was <10.0. Loss of primary patency was seen in three post-thrombotic patients, in all cases rethrombosis occurred (Figure 8).

Residual compression in one patient with a history of a spondylodesis by metal rods and screws led to quick stenosis and thrombosis of the stented common iliac vein.

Figure 7. Kaplan Meier analysis of patency rates of (A) the total population, (B) the iliac vein compression syndrome population, and (C) the PTS population.

Figure 8. Loss of patency cases. (A) X-ray in lateral projection showing sub-optimal stent configuration because of extensive spondylodesis material leaving a remaining compression (white arrow). (B) Cone beam CT imaging showing significant stent compression, non-responding to repeated balloon angioplasty. (C) Completion angiography after stenting for post-thrombotic iliac vein obstruction showing a gap between stent segments at the level of the overlying common iliac artery resulting from sub-optimal deployment technique. (D) Cone beam CT imaging showing persistent compression caused by lack of stent material and therefore crush resistance at the level of the common iliac artery (white arrow). (E) Adequate surface area after re-stenting.

This was treated by catheter directed thrombolysis followed by re-stenting of the CIV with a high radial strength balloon expendable stent (Andrastent XL 43 mm, Andramed, Reutlingen, Germany). In a second patient the stent placed in the CIV was mistakenly stretched during placement, leading to a significant gap between the struts of the stent; at this point the right common iliac artery slipped into the gap causing a persistent stenosis during follow up. This was treated by restenting with a second well placed sinus Venous stent. In the third patient, with a history of IV drug abuse into the common femoral vein, the fibrotic vein was not predilated with enough pressure. During follow up, significant stenosis was seen at this level, which was treated solely using high pressure rePTA. Other complications during follow up are noted in Table 10.

Table 10. Complications after stent placement.

Complications	Total population		PTS		IVCS	
N	75		40		35	
Proximal stent extension into vena cava	3	4%	1	3%	2	6%
Minor bleeding during admission	1	1%	1	3%	0	0%
Stent related pain needing readmission	1	1%	1	3%	0	0%
Residual stent compression	2	3%	2	5%	0	0%
Stent tapering	2	3%	2	5%	0	0%
Stent stenosis	2	3%	2	5%	0	0%
Anticoagulation related minor bleeding during follow-up	4	5%	4	10%	0	0%
Stent placed proximally of common iliac vein	3	4%	2	5%	0	0%

Clinical improvement

Median Villalta score in the PTS group decreased from 11.5 (2-24) before treatment to 5.0 (0-16) at last follow-up, which constituted a decrease of 6.5 (p .001). VCSS decreased 3 points, from 8 (3-21) preintervention to 5 (0-16) at last follow up in the PTS group and decreased 2 points from 6 (2-19) to 4 (1-16) in the iliac vein compression group, both decreases were statistically significant (p .001 and p = .019). Venous claudication subsided in 18 out of 25 patients in the PTS group (p .0001) and in 14 out of 16 patients in the iliac vein compression group (p = .0002). Two of four ulcers healed in the PTS group, and none healed in the iliac vein compression group. Both healed ulcers recurred during follow up.

DISCUSSION

In this study, short-term results for use of the segmental sinus Venous stent in chronic venous obstructive disease are very favorable, both in the post-thrombotic syndrome

and iliac vein compression syndrome. In a previous study, initial data on PTA and stenting in a similar population from the same center were presented.³ In both studies, PTA and stenting were shown to be safe and feasible when using self-expandable nitinol stents with good patency rates, mild complication rates, and no mortality. Other authors have shown similar favorable results of deep venous stenting during recent decades, including those series in which patients were stented with other stent types, especially the Wallstent (Boston Scientific).^{1,16,17} As the Wallstent suffers from significant foreshortening, precise positioning is sometimes difficult in inexperienced hands and occurrence of skip lesions may occur. Therefore, earlier reports mentioned the need for considerable overlapping of multiple stents to prevent incomplete treatment of obstructive lesions. Multiple centimeter overlaps make the stented segment even more rigid. Furthermore, to prevent retrograde migration the Wallstent has to be placed well into the inferior vena cava, potentially impairing contralateral outflow and increasing the risk of contralateral iliac vein thrombosis. Arterial designed nitinol stents have their own shortcomings and differ from venous designed stents in several ways.

Firstly, the diameter of a vein is greater than that of an artery. This is particularly important in the common iliac tract as generally stent diameters of 16-20 mm are needed. Arterial stents are generally not offered in these diameters.

Secondly, post-thrombotic obstructions generally cover a greater length of the vein compared with arterial obstructive lesions. Therefore, more than one stent is often required in post-thrombotic patients when using arterial nitinol stents. The increased overlapping areas of the stents further reduce flexibility.

Thirdly, post-thrombotic veins are often heavily scarred and have firm intraluminal fibrotic strands, which may extend over relatively long segments. Predilatation, sometimes with high pressure balloons, is needed to break these fibrotic strands and dilate the fibrotic vein wall. A stent with sufficient resistive radial force is needed to maintain this diameter. This force in arterial designed stents is most often insufficient. In iliac vein compression syndromes the local pressure on a vein caught between the overlying artery and bony structures is high, and therefore calls for stents with sufficiently high resistive radial force.

Fourthly, in contrast to arteries, normal veins have a less supported wall and are more susceptible to external forces. Post-thrombotic veins might be influenced less because of the fibrotic changes. Nevertheless, it is generally recommended to land a stent in a healthy vein segment. It is therefore conceivable that particular stent properties have an effect on the integrity of the vein at this location. Optimally, stents implanted within venous structures should be able to move effortlessly with every movement of the vein. Stents with excessive rigidity might dictate the shape of the vein, thereby perhaps creating suboptimal hemodynamics or damage to the vein wall causing stenosis,

occlusion, or insufficient flow. This is especially the case when stents cross the internal iliac vein and inguinal ligament where sufficient flexibility is most important.¹⁸ Finally, when a highly rigid stent is forced to maintain its position at two locations, there is an increased risk of kinking which might lead to stenosis (Figure 9).

Figure 9. Arterial stent design (sinus XL stent, OptiMed GmbH, Ettlingen, Germany), versus dedicated venous stent design (sinus Venous stent, OptiMed GmbH, Ettlingen, Germany). (A) Forcing an arterial designed stent into a curve increases the risk of kinking. (B) Dedicated venous stents can be shaped easily into an “S” curve. (C) Oblique projection X-ray post stenting with arterial designed stents showing kinking on the left (white arrow) and straightening of a stent-in-stent on the right (black arrow). (D) “S” shape of a venous stent to treat a May-Thurner compression, adapting perfectly to the venous anatomy.

In the authors’ opinion, an optimal venous stent should be able to flex at two different points without narrowing at these flex points (Figure 9), thereby preventing kink related stenosis. In general, the venous anatomy should therefore dictate the shape

of the stent and not vice versa. The sinus Venous stent should prevent kinking by its segmental design. Connecting rings with close-cell design creates a high radial force. Connecting the rings with two tiny connections keeps the system sufficiently flexible (Figure 10). However, a number of concerns exist. Most importantly, at the level of the highest external force the stent segments should be placed in close proximity, to avoid a high pressure point exactly between segments, which makes delivery technically challenging, with the most important being the pressure point at the level of the overriding common iliac artery. A more or less oval shape can be seen at these levels of high compression, but a residual stenosis of more than 50% would be unacceptable. Other stented segments do not seem to suffer from focal pressure points. Also, the “bare areas” left between separate rings do not appear to predispose to restenosis, at least during the first year, as shown in this study.

Figure 10. 3D CT reconstruction, antero-posterior (A) and oblique (B) after stenting of the left common and external iliac vein clearly showing the segmented stent design and curved configuration at the level of the internal-external iliac vein confluence and at the level of the common femoral vein, locations known to be prone to kinking or residual compression.

As shown by Neglén et al., significant differences in outcome can be observed when comparing stenting for thrombotic and non-thrombotic disease.¹ In this series similar differences were observed; no stents occluded in the iliac vein compression subpopulation, and all three loss of primary patency instances were seen in the PTS group. The higher number of reocclusions in this group might be caused by the etiology and severity of PTS and compromised venous inflow from femoral veins resulting from extensive post-thrombotic trabeculations. Limitations of this study include the small population with short median follow up. Moreover, an in depth comparison with the use of other stents, especially the Wallstent, has not been performed.

CONCLUSION

Short-term clinical results using the sinus Venous stent are excellent, with significant symptom reduction, low morbidity rates, and no mortality. Stent related loss of patency is seen infrequently. Post-thrombotic lesions showed a lower patency compared with non-thrombotic lesions, a known reported finding.

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CHAPTER 5

ILIOCAVAL CONFLUENCE STENTING FOR CHRONIC VENOUS OBSTRUCTIONS

Rick de Graaf¹

Mark de Wolf²

Anna M. Sailer¹

Jorinde van Laanen²

Cees Wittens^{2,3}

Houman Jalaie³

¹ Department of Radiology, Maastricht University Medical Centre, Maastricht, The Netherlands

² Department of Vascular Surgery and Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands

³ Department of Vascular Surgery, University Hospital RWTH Aachen, Aachen, Germany

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ABSTRACT

Purpose

Different techniques have been described for stenting of venous obstructions. We report our experience with two different confluence stenting techniques to treat chronic bi-iliocaval obstructions.

Materials and Methods

Between 11/2009 and 08/2014 we treated 40 patients for chronic total bi-iliocaval obstructions. Preoperative magnetic resonance venography showed bilateral extensive post-thrombotic scarring in common and external iliac veins as well as obstruction of the inferior vena cava (IVC). Stenting of the IVC was performed with large self-expandable stents down to the level of the iliocaval confluence. To bridge the confluence, either self-expandable stents were placed (24 patients, SECS group) or high radial force balloon-expandable stents were placed at the same level (16 patients, BECS group). In both cases, bilateral iliac extensions were performed using nitinol stents.

Results

Recanalization was achieved for all patients. In 15 (38 %) patients, a hybrid procedure with endophlebectomy and arteriovenous fistula creation needed to be performed because of significant involvement of inflow vessels below the inguinal ligament. Mean follow-up was 443 ± 438 days (range 7–1683 days). For all patients, primary, assisted-primary, and secondary patency rate at 36 months were 70, 73, and 78 %, respectively. Twelve-month patency rates in the SECS group were 85, 85, and 95 % for primary, assisted-primary, and secondary patency. In the BECS group, primary patency was 100 % during a mean follow-up period of 134 ± 118 (range 29–337) days.

Conclusion

Stenting of chronic bi-iliocaval obstruction shows relatively high patency rates at medium follow-up. Short-term patency seems to favor confluence stenting with balloon-expandable stents.

INTRODUCTION

Recanalization and stenting of chronic deep venous obstructions is a minimally invasive intervention that has proven effective and safe over the last decades [1]. With low complication rates and substantial clinical improvement, this procedure has been increasingly performed over the last years. Long-term stent patency rates however vary substantially between clinical reports. Although encouraging 92 % stent patency after 10 years has been reported by dedicated highvolume centers [2, 3], lower results were published by clinics with lesser numbers of patients [4, 5]. Partly, this variation might be explained by lack in dedicated venous interventional tools, e.g., stents. However, in recent years, a lot has changed both in interventional materials and techniques, which might be vital to achieve an optimal result. Therefore, it is of great importance to report on experience with new developments in stent design and stenting technology to help establish an optimal protocol, both for defining the right indication and choosing the optimal treatment.

Chronic vena cava obstruction can stay asymptomatic for a long time. Extensive collateralization through paralumbar veins and the azygos system might obscure the underlying hemodynamic severity for many years into adulthood. However, many patients will be confronted with decompensation at some point in their life, which becomes clinically evident by acute, and in many cases bilateral deep venous thrombosis (DVT). Reconstruction of the occluded inferior vena cava (IVC) by means of angioplasty and stent placement has been performed previously with satisfactory to excellent results [6–8]. However, stenting of the common iliac vein confluence has only been thoroughly described by Neglén et al. [9]. In their study, different stenting techniques were suggested to reconstruct the iliac confluence, all with their own limitations. In this article, we describe our experience with two confluence stenting techniques, one with merely self-expandable stents, the other with balloon-expandable stents bridging the common iliac vein confluence.

Materials and Methods

From November 2009 to August 2014, 741 patients were evaluated for chronic venous insufficiency/post-thrombotic syndrome (CVI/PTS) or acute central venous obstructive complaints at our tertiary medical center. Forty of these patients were diagnosed with chronic ilio caval obstruction. Chronic ilio caval obstruction was defined as 50 % or more venous lumen obstruction [10] of the IVC involving the confluence on Duplex ultrasound (DUS) or magnetic resonance venography (MRV) with presence of post-thrombotic trabecular changes in both common iliac and external arteries. All patients received DUS and MRV before treatment and cases were discussed in a multidisciplinary team consisting of a venous vascular surgeon, interventional radiologists, a dedicated ultrasonographer and experienced nurses.

All procedures were performed under general anesthesia and full anticoagulation. Patients were administered at least one dose of 5000 IU of heparin during the procedure. After the intervention, patients received a single dose of Low-Molecular-Weight Heparin (LMWH, Tinzaparine) and the preintervention anticoagulation regiment was continued, in general aiming for an international normalized ratio (INR) of 3.0–4.0. Patients who did not receive preinterventional anticoagulation were started on coumarins directly poststenting aiming for the same INR range, they received daily LMWH's until this INR range was achieved (with a minimal treatment time of at least 5 days). When no underlying thrombophilia was proven, anticoagulation therapy was continued for at least 6 months.

Stenting Technique

Patients with IVC and bilateral iliac vein obstruction and debilitating complaints interfering with daily life (most often chronic pain and/or venous claudication), with or without skin changes or ulceration (CEAP C4–6) were offered stent placement. Patients with IVC and bilateral iliac vein obstruction and acute bilateral DVT were also indicated for stenting. Procedures were performed in a dedicated angio suite or hybrid OR. Venous access was obtained through the femoral vein, at least 15 cm distally to the deep femoral inflow under ultrasound guidance. This access site was chosen to obtain optimal angiographic evaluation about the inflow from the deep femoral vein and the collateral network as well as to provide a sufficient distance to the landing zone for stenting. The technique for traversing stenotic and occluded venous segments has been described before [11]. After successful recanalization thorough predilation was done up to 25 mm for the IVC and 14–16 mm for the external and common iliac vein. Due to the elasticity of the lesions, all pathologic venous segments that are being predilated should generally be stented. Based upon the design of the stents used to treat diseased vein segments, we gained experience with two stenting protocols. In our earlier experience, stenting was performed with nitinol self-expandable stents to treat the entire diseased venous segments from the vena cava down to the external iliac vein (SECS group; (Figure 11). These self-expandable stents (sinus XL, Optimed, Ettlingen, Germany) are registered for treatment of vena cava obstructions, because of the large diameters available and their high crush resistance. In all cases, the vena cava was stented with a diameter of 24 mm. Bilateral extensions were performed with 16 mm nitinol stents (sinus XL, sinus Venous and sinus XL-flex, Optimed, Ettlingen, Germany and Zilver Vena (Cook, Galway, Ireland), which were placed parallel inside the vena cava stent with a 2 cm overlap (Figure 11).

In order to minimize stent strut interactions at the confluence, an alternative technique was used where two balloon-expandable stents (AndraStent, Andramed, Reutlingen, Germany) were placed in the vena cava stent toward the common iliac veins (BECS group; Figure 12). Bilateral iliac extensions were then performed with 16 mm nitinol

stents (sinus Venous or Zilver Vena stents). In both groups, postdilation of the entire stented segments was always performed using a balloon with same diameter as the stents implanted. Inflation time was kept to a minimum, with the sole purpose to let the stents deploy completely. In cases of incomplete deployment, high pressure balloons were used to reach full deployment. Poststenting angiography was done by means of Conebeam CT imaging (AlluraClarity, Philips Healthcare, Eindhoven, The Netherlands) to evaluate stent expansion and apposition (Figure 12).

Figure. 12 Confluence stenting with self-expandable stents (SECS). A– C self-expandable stents are placed within the large diameter IVC stent, extending into the common and/or external iliac veins. D CT shows compression of one iliac self-expandable stent, while the adjacent stent shows adequate expansion. E peroperative conebeam CT shows another example of significant compression by the contralateral stent.

Figure 12 Confluence stenting with balloon-expandable stents (BECS). A preoperative MR venography shows an IVC remnant (arrow). Notice the post-thrombotic scarring in the external iliac vein (arrowhead). Asterisk aorta. B angiography shows severe obstruction of bilateral iliac veins and no filling of the IVC. C after iliac recanalization angiography from the level of the confluence shows an adjacent stent shows adequate expansion. E preoperative conebeam CT shows another example of significant compression by the contralateral stent long stenosis in of the IVC. D and E positioning and deployment of two balloon-expandable stents. F completion angiography shows excellent flow from both iliac limbs through the newly constructed iliac confluence and IVC. G–I Conebeam CT reconstructions showing perfect positioning and expansion of the stents at the confluence and IVC

Endophlebectomy and arteriovenous fistula creation

Extension of post-thrombotic changes at the level of the femoral vein inflow was seen in 15 (38 %) patients. The decision to perform adjunctive surgical desobstruction was preoperatively made based on MRV imaging. When trabeculations were visible in the common femoral vein extending to both the femoral and the deep femoral (profunda) vein, peripheral venous inflow was deemed insufficient. Use of MRV imaging for evaluation of severity and extent of the disease (trabeculations) proofed consistent during surgery meaning desobstruction was performed in all the selected cases. In these 15 patients, a hybrid procedure consisting of endovascular recanalization and stenting combined with surgical groin incision, endophlebectomy, and creation of an

arteriovenous fistula (AVF) was performed to optimize inflow and secure short-term stent patency. In the other 25 patients where no post-thrombotic changes at level of the deep femoral vein inflow were seen, merely recanalization and stenting was performed.

Postoperative stent patency was evaluated by DUS. All patients received follow-up according to a strict protocol consisting of DUS imaging 1 day postintervention, 2 and 6 weeks after the intervention as well as 3, 6, and 12 months after the intervention and annually thereafter, or if recurrence of symptoms required earlier evaluation. Patency was defined as patency of more than 50 % of the venous lumen on DUS. Direct postinterventional as well as 2 and 6 week DUS examination enabled us to perform timely catheter directed thrombolysis in case of acute reocclusion.

Statistical Analyses

Categorical data are presented by frequencies and percentages. Continuous data are expressed by mean or median values with range and standard deviation. Kaplan–Meier survival analysis was used to calculate patency rates per extremity for all patients (80 legs) as well as for the endovascular only group (50 legs); (Graphpad prism version 5.00 for Microsoft Windows, Graphpad Software. San Diego, CA). Survival percentages with a standard error of the mean (SEM) of >10 % were discarded as being unreliable.

RESULTS

Patient Demographics

The patient group consisted of 24 female and 16 male with a mean age of 41 ± 14.9 years (range 16–62 years). MRV determined IVC obstruction with complete certainty in 100 % of cases. In all cases, intraluminal changes, i.e., trabeculations were seen, suggestive of post-thrombotic fibrosis due to earlier DVT. In 6 (15 %) patients, no clinically obvious DVT was noted in their medical history, but the combination of DUS and MRV showed post-thrombotic changes in the venous system in all of these patients. Patients were treated on average 12 ± 8.5 years (range 2–27) after their first DVT. Clinical signs, as scored in the CEAP classification, are shown in Table II.

Acute bilateral DVT was the indication for treatment in 6 (15 %) patients, skin changes and ulceration in 18 (45 %) patients, venous claudication in 15 (38 %) patients, and chronic lower extremity pain without claudication in one (3 %) patient.

Table II Overview of CEAP clinical classification [16] for the study population (40 right and 40 left legs)

CEAP C Class	Right leg	Left leg
C0	1 2.5 %	3 7.5 %
C1	5 12.5 %	5 12.5 %
C2	7 17.5 %	7 17.5 %
C3	11 27.5 %	10 25 %
C4	9 22.5 %	9 22.5 %
C5	4 10 %	4 10 %
C6	3 7.5 %	2 5 %

Interventions

All 40 patients with ilio caval obstructions were recanalized successfully. The average length of vena cava occlusion was 13.8 (range 5–21) cm. The average total length of ilio caval obstruction was 31.2 cm (range 24–37). No perprocedural bleedings or other complications were encountered. In 24 patients, self-expandable stents were used to construct the confluence (SECS group), while in 16 patients a combination of balloon-expandable and self-expandable stents was used (BECS group).

Follow-up

Mean time until latest DUS follow-up examination was 443 ± 438 days (range 7–1683 days). In 33 (82 %) patients, the vena cava and both iliac veins were patent at latest follow-up. In four (10 %) of the patients with stent reocclusions, one of the iliac veins was occluded at latest follow-up, while the contralateral side and vena cava remained patent. One patient showed total occlusion of the stented area, however clinical signs remained mild during follow-up, possibly because of a well-developed collateral network, reintervention was therefore postponed indefinitely. Moreover, secondary patency after reocclusion was obtained by sole thrombolysis in three and catheter-directed thrombolysis combined with restenting in another three patients (in one also an AVF was created), in one patient a deep venous bypass was created surgically. This leads to patency rates of treated lower extremities at 12 months of 79, 82, and 90 % (SEM 5.6, 5.5, and 3.8), and at three years of 70, 73, and 78 % (SEM 6.9, 7.1, and 9.0), for primary, assisted-primary, and secondary patency, respectively (Figure 13A).

Figure 13. Kaplan–Meier analyses of primary and secondary patency of lower extremities in the total population (80 legs) and the cases treated by endovascular means only (50 legs)

Specific analysis of the population treated by endovascular means only (without endophlebectomy and AV-fistula creation) shows higher patency rates. Twelve-month patency rates in the SECS group were 85, 85, and 95 % for primary, assisted-primary, and secondary patency, respectively (Figure 13B). In the BECS group, primary patency was 100 % during a mean follow-up period of 134 ± 118 (range 29–337) days (Figure 13B). Observed complications did not lead to long-term impairment (Table 12). Although reocclusions occurred, no patients reported worsening of their symptoms.

Table 12 Overview and quantification of complications observed in 40 patients treated with caval-bi-iliac recanalization and stenting

Complication	Frequency	%
Reocclusion in one or both iliac veins or IVC	10 ^a	25.0
Significant stenosis due to AVF	4	10.0
Major bleeding	3	7.5
Minor bleeding	3	7.5
Lymph leakage/lymphocele	3	7.5
Stenosis deemed non-hemodynamically significant	7	17.5
Residual compression	3	7.5
Tapering	5	12.5
Stent kinking	1	2.5
Stent fracture	1	2.5

^aSix patients treated by catheter directed thrombolysis

DISCUSSION

The etiology of IVC obstruction has not yet been determined completely. A congenital origin has been proposed [12]. Central line placement and subsequent thrombosis in premature life might be another explanation [13]. In the present study population, only two patients had endured such an intervention. Sudden IVC thrombosis in later life might develop in case of compression by benign or malignant masses or adjacent anatomic structures. However, we did not see such underlying pathology in our patient population. True absence of the IVC has also not been noticed in our group of 741 patients evaluated for signs of deep venous obstruction between 2009 and 2014. Although this might be suspected on angiography because no contrast dye is seen in the extent of the IVC, MRV always showed a visible remnant (Figure 12A–C).

Iliac vein and IVC stenting has been performed successfully since more than a decade, has proven to be effective and is considered the first line of treatment in chronic venous obstructive disease [14]. Nevertheless, experience was limited to a small number of centers for many years, with the group of Neglén et al. reporting on the largest number

of patients by far [3, 9, 15]. Recently, recanalization and stenting of chronic venous obstructions became more widespread and probably will increase to mature in years to come. Although the endovenous approach has been suggested straightforward, innovative materials enable us to explore alternative approaches, which might reduce complications and improve results. Specifically, for confluence stenting, only few techniques and stent configurations have been proposed, mainly due to limitations in stent design. In the vast majority, the Wallstent™ (Boston Scientific) was selected as the stent of choice, which limited stent configuration options. However, with the introduction of nitinol and cobalt–chromium stents appropriate for use in the venous system, other techniques have become available. We discuss our fenestration technique, the ipsilateral stent is pierced and the contralateral limb is then maneuvered through this fenestration. The confluence technique is performed by large diameter stents in the IVC. With a small overlap, two balloon-expandable or self-expandable stents are used as an extension into both iliac veins experience and patency results with these stents to treat bilateral ilio caval obstruction by means of confluence stenting.

5 We used two different techniques to construct the new confluence. In our earlier cases, we placed two self-expandable stents within a wide-diameter stent positioned in the distal vena cava just above the confluence, which were extended distally as far as required. With the help of perprocedural rotational angiography and coincidental CT examinations, it was noted though that stent compression was a main issue (Figure 11). When two self-expandable stents are placed within a restricted space, one is likely to become greater in diameter than the other one, thereby compressing the contralateral side which is corroborated in the diminished short-term patency in the SECS group. Thus, we decided to optimize our protocol by bridging the confluence with two ultrastrong parallel positioned balloon-expandable stents. The BECS group showed a 100 % short-term primary patency. Although the present confluence technique has been mentioned before, no clear description of the technique and interventional tools were given. Furthermore, specific outcome data were not discussed [6].

Other stenting techniques to treat the common iliac vein confluence have been described earlier [9]. Neglén et al. evaluated three techniques to perform bilateral stenting at the ilio caval confluence (Figure 14). In our opinion, both the fenestration and apposition technique should be considered inferior to the confluence technique. The fenestration technique requires purposeful fracturing of the contralateral iliac stent, which increases the risk of complications like balloon rupture and subsequent entrapment of devices. Furthermore, reinterventions like thrombectomy might be hampered, which is also true for the apposition technique. Confluence stenting with balloon-expandable stents helps overcome potential problems related to reinterventions. Finally, recreation of the iliac confluence generates flow dynamics that might alternative technique to create an efficient and safe true confluence configuration (Figures 12, 14). Based upon our experience, we suggest the BECS technique to be superior to treat chronic bilateral

iliocaval obstructions. It should however be noted that the BECS technique might not be the best option in women at child bearing age, since these stents may non-reversibly compress during pregnancy or birth.

Figure. 14 Techniques to treat caval-bi-iliac venous obstruction. The double barrel technique is performed by placing two parallel stents into the IVC as an extension from both iliac veins. In the apposition technique, the ipsilateral iliac stent is extended into the IVC while the contralateral iliac stent is placed in close contact to the former. In the fenestration technique, the ipsilateral stent is pierced and the contralateral limb is then maneuvered through this fenestration. The confluence technique is performed by large diameter stents in the IVC. With a small overlap, two balloon-expandable or self-expandable stents are used as an extension into both iliac veins.

There are some limitations to our study. First, the observational design of the study makes it difficult to draw strong conclusions toward the optimal confluence stent technique. However, availability of stents on the market precluded the possibility to perform a randomized design of the study. Nevertheless, our experience adds to the knowledge of venous stenting thus far reported and might aid in the process of product development and treatment protocols. Secondly, we used different stents to make peripheral extensions from the confluence toward the groin. In the beginning, we used nitinol closed-cell stents in the iliac veins. Since 2013, “dedicated venous stents” were used. “Dedicated” means that the stent manufacturer implies that the stent is better accommodated to the venous anatomy. Usually, these stents are larger in diameter, show good flexibility and high hoop force. Although these venous stents are supposed to perform better in the venous vasculature, up to now there is no proof that these stents improve outcome. Therefore, we have to conclude that the differences in patency between the SECS and BECS group are more likely based upon the configuration of confluence stenting. Based upon our experience with stenting across the common iliac vein confluence, we suggest preferable stenting technique to treat bilateral ilio caval obstructions. Preservation of bilateral symmetric inflow, protection of stent integrity, and avoidance of abundant stent material at the level of the confluence suggest that the BECS technique is superior to earlier described techniques. Evolution however is continuing, and we await the development of “confluence-stent” devices that have already been recognized in bifurcated aorta repair and might also support venous reconstructions.

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CHAPTER 6 INDICATIONS FOR ENDOPHLEBECTOMY AND/OR ARTERIOVENOUS FISTULA AFTER STENTING

M.A.F. de Wolf^{1,2}

C.W.K.P. Arnoldussen³

C.H.A. Wittens^{1,2,4}

¹ Department of General Surgery Maastricht University Medical Center (MUMC), Maastricht, the Netherlands;

² Cardiovascular Research Institute (CARIM), Maastricht, the Netherlands;

³ Department of Radiology MUMC, Maastricht, The Netherlands;

⁴ Department of Vascular Surgery University Hospital Aachen, Aachen, Germany

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ABSTRACT

Endovenous recanalization with percutaneous transluminal angioplasty and stenting in post-thrombotic syndrome patients with ilio caval obstruction is a treatment modality quickly gaining popularity. Studies show good patency and clinical success rates. If the obstruction extends distally, below the inguinal ligament, stenting remains controversial. Without adequate inflow, the patency of stented ilio caval segments drops dramatically. This suggests that treatment of diseased common femoral, femoral and profunda femoral veins is required to ensure adequate inflow. Endophlebectomy, the removal of synechiae and septae from the common femoral vein, is a viable option in these cases. Another option, which can be done concurrently with the endophlebectomy, is the creation of an arteriovenous fistula. Selecting patients for these interventions however remains difficult, as precise preoperative prediction of inflow into the stented segments is difficult. In this paper we describe our experience in using duplex ultrasonography, magnetic resonance venography and conventional venography to assess the patency of the inflow trajectory. We believe this approach is essential in dealing with cases of complex post-thrombotic disease extending below the inguinal ligament. There is a great need to establish criteria to accurately assess pre- and postinterventional flow through treated vein segments.

INTRODUCTION

Although arterial percutaneous transluminal angioplasty (PTA) and stenting were first described in 1964 by Charles Dotter and in 1985 by Palmaz et al.^{1 – 3} respectively, and the first endovenous stenting already described in 1986, endovascular recanalization and stenting of the deep venous system has only recently gained widespread interest and use. This is partly due to disappointing early results, the lack of interest in the post-thrombotic syndrome (PTS) and the unawareness of the relationship between PTS severity and the location and extend of deep venous thrombosis.⁴ Currently the number of patients treated with deep venous PTA and stenting is increasing exponentially, because of published good clinical results, improved patency rates and low mortality and morbidity rates.^{5 – 9} Neglén et al.⁷ showed good overall long-term results, but lower patency rates in cases of post-thrombotic disease compared with non-thrombotic disease. This might be explained by the changed anatomy of post-thrombotic veins, characterized by rigidly scarified vessel walls and intraluminal synechiae and septae, which also create a thrombogenic environment.¹⁰ This thrombogenic environment can be treated, both pre and poststenting, by adequate anticoagulation, either with Coumadins, low-molecular-weight heparins or new oral anticoagulants.^{11 – 13} In order address the changed anatomy one needs to recanalize a post-thrombotic diseased segment. Various guidewires are needed to pass the synechiae and septae after which an angioplasty, mostly with high pressure balloons, is needed before stent placement.¹⁴ After stenting the restored patency of the treated caval and/or iliac vein segments should redirect flow through this normal anatomical route and decreases or resolve flow via previously developed collateral veins. This technique has been described previously.¹⁴ However, in case of femoral involvement in post-thrombotic disease, venous inflow into the to-be-stented ilio caval segments is frequently inadequate. Obstruction or occlusion in the common femoral vein can impair outflow of the femoral, deep femoral and great saphenous vein into the stented segment, causing a low flow through the stented segment. As low flow conditions relate strongly with thrombosis and reocclusion, this needs to be addressed. However, stent placement in the common femoral and femoral segments is still under debate.¹⁵ Too effectively, minimally invasively, guarantee adequate inflow from all three, femoral, deep femoral and great saphenous, veins into the stented segment above the saphenofemoral junction (SFJ) a branched stent has to be developed. Without this theoretical opportunity there is always the chance of not being able to cross the different intraluminal planes created by the septae in the common femoral vein. In such a case one would, e.g. only recanalize a portion of the vein and inflow might only be restored from one of the three veins connected to the common femoral vein. Besides this technical problem, we know from arterial stenting across joints that stent fractures may occur,¹⁶ although Neglén et al.¹⁵ showed that stent elongation across the inguinal ligament is safe using Wall stents (Boston Scientific, Natick, MA, USA). Other authors are generally less aggressive in stent placement across joints, especially when Nitinol stents are used, which have a greater tendency to

fracture when stressed.

Alternatively the obstruction or occlusion of the common femoral vein can be addressed in a surgical manner, which is termed endophlebectomy, endovenectomy or desobstruction.^{10,17,18} This technique was first described by Gloviczki in 1999 in relation to venous bypass surgery. Raju et al.¹⁹ showed feasibility in 1999 in cases of axillary vein transfer and Puggioni et al.¹⁰ in 2004 in cases of deep venous reconstruction. Summarized endophlebectomy entails: the post-thrombotic damaged common femoral vein is longitudinally opened and the intraluminal senechia and masses are removed. Any post-thrombotic lesions obstructing outflow from the femoral, deep femoral or great saphenous vein need to be removed and inflow into the common femoral vein restored. The venotomy can be primarily closed or by using a patch, in case of a narrowed lumen. This should guarantee physiological inflow into the stented segments. It is vital that the distal end of the stent should at least extend into the 'cleaned' common femoral vein segment. After restoration of the physiological flow combined with adequate anticoagulation, there still might be a highly thrombogenic local environment at the level of endophlebectomy or stents, caused by both surgical damage to the vessel wall and the stent material. This is why an endophlebectomy is frequently combined with the creation of an arteriovenous fistula (AVF) in order to increase flow in the treated area and theoretically reduce the chance of thrombosis.^{10,18,20 – 22} In our center a loop with a 6 mm externally supported polytetrafluoroethylene (PTFE) graft of about 6 – 8 cm long is created between the common femoral artery and vein. We learned that native fistulae are too small or when created with a diameter larger than 5 – 6 mm they need to be closed (surgically) after six months because of persistent swelling of the leg. The advantage of using a PTFE loop is that it guarantees a high flow rate in the first months and that it can be percutaneous closed, e.g. with an Amplatzer Vascular Occluder (AGA Medical Corporation, Plymouth, MN, USA).^{23,24} When PTA, stenting, endophlebectomy, AVF and adequate anticoagulation are combined in these complex and extensive cases of PTS, all three facets of Virchow's triad (blood, flow and vessel) are addressed.

To our knowledge no effective and validated diagnostic tests, and their cut-off values, are currently available to pre- or peri-intervention quantify haemodynamic parameters associated with patency rates after deep venous stenting in order to help us decide if there is an indication for an endophlebectomy with or without an AVF. Ideally such a test should measure flow at the in- and outflow site of the stented segment. At this moment only anatomical parameters, acquired by or duplex ultrasonography (DUS), ascending venography, magnetic resonance venography (MRV), computed tomography venography (CTV) or intravascular ultrasonography (IVUS) are used to indicate if patients are eligible for endophlebectomy and/or AVF.^{25,26} These parameters include location and extend of post-thrombotic lesions, percentage of lumen reduction, and number and extend of collateral veins. In this paper we described current literature

and our own experience in the challenge of diagnosing (in)adequate venous flow in post-thrombotic deep veins and indicating patients for ancillary surgery combined with or after PTA and stenting.

Imaging characteristics of patients undergoing endophlebectomy and arteriovenous fistula

Patients with chronic venous disease in which a deep vein obstruction is suspected require adequate analyses of the deep venous system. Besides clinical examination, e.g. abdominal wall venous collaterals and in some centers functional tests, e.g. plethysmography, a crucial part of this analysis is imaging.²⁷ The initial imaging modality of choice should be duplex ultrasound.^{28,29} The primary objective is the assessment of the presence and the extent of any deep venous reflux, signs of recanalization and/or flow impairment, luminal narrowing and vein wall thickening. The veins that need to be examined are the popliteal, femoral, deep femoral and common femoral vein. Additionally, collaterals in the groin and signs of obstruction in the pelvis should be identified. When there are signs of obstruction with collateralization in the groin and/or pelvis, additional imaging should be performed. The aim of this additional imaging should be to accurately assess the extent of the obstruction, reconstruct the anatomy of the inferior vena cava and the common and external iliac veins and assess the routes of collateralization to assess the extent of the diseased tract. Furthermore, imaging should quantify the chronic, mostly post-thrombotic, vein abnormalities in both the inferior vena cava and iliac veins, as well as the common femoral, deep femoral and femoral vein. In a non-invasive setting, the choice of examination is either MRV or CTV. In our experience, both techniques are capable of identifying obstruction and collateralization, but only MRV is capable of accurately detecting intraluminal post-thrombotic changes, which affect our treatment decisions as we described with the LOVE score (Figures 15 and 16).²⁵ In our treatment approach, conventional venography and IVUS are reserved for those patients in whom we have decided to perform an endovascular recanalization and stenting, since these are invasive procedures that require a hospital admission.

Figure 15. Magnetic resonance venography image in the transverse plane showing the chronically diseased common femoral vein (CFV) in a patient with a post-thrombotic syndrome with an occluded right external and common iliac vein. The arrow marks trabeculations within the CFV as a result of poor recanalization which suggest impaired inflow to the iliac veins

Figure 16. Magnetic resonance venography image in the coronal plane showing a chronically diseased common femoral vein and external iliac vein with trabeculations. Multiple trabeculations can be identified suggesting flow impairment over these segments

In chronic deep venous obstruction, roughly four patterns of disease can be identified. The first pattern is isolated obstruction at the level of the common iliac vein, in virtually all cases associated with compression (May–Thurner syndrome). In these patients there are usually no, or minimal post-thrombotic changes in the external iliac and femoral veins. The second pattern is obstruction of both the common and external iliac vein. In these patients the patterns of collateralization are more extensive and usually the groin shows signs of collaterals with relatively mild or unscarred femoral veins. The third pattern shows occlusion of the common and external iliac vein with involvement of the femoral veins. Collateralization is prominent in these cases, but more importantly severe scarring of the common femoral vein, often combined with impaired recanalization of the femoral and deep femoral vein, is seen. The fourth pattern shows involvement of the inferior vena cava, usually with extensive paralumbar collateralization and hyperplastic azygos and hemiazygos veins. In these cases disease in the iliac and femoral veins can either be symmetrical showing pattern 1, 2 or 3 on both sides or asymmetrical, usually related to the occurrence of deep vein thrombosis in the past.

Patients who present with isolated common iliac vein obstruction can be effectively treated with endovascular recanalization and stenting.^{5–8,14,21,22} Also in patients with a common and/or external iliac vein obstruction, without common femoral vein involvement below the SFJ endovascular recanalization and stenting can be performed without additional surgical intervention. In patients with a common and/or external iliac vein obstruction with common femoral vein involvement below the SFJ we perform an endophlebectomy. In most cases, in addition to the involvement of the common femoral vein, the femoral and deep femoral vein are also involved in which case we perform an endophlebectomy with an AVF. Lack of inflow into the stented segment, due to the preexisting inflow impairment from the deep femoral and femoral

vein, combined with an increased thrombogenic post-thrombotic common femoral vein cause these patients to be at increased risk for in-stent thrombosis due to lack of flow.

In patients where the IVC is involved we decide on our treatment approach based on the extent of the involvement of the vena cava as well as the iliac and femoral axis. In isolated infrarenal IVC involvement an antegrade approach from either the groin or femoral vein usually suffices. In those cases where the suprarenal IVC is involved, access from the jugular vein can be helpful in which case patient positioning and procedure planning is adjusted. By utilizing all our preoperative imaging information as described above we can accurately select patients for what we believe will prove to be the most optimal approach of treating chronic venous obstructions.

At the end of the procedure it is crucial to assess the preferential outflow pattern. In patients with isolated iliac disease, collaterals identified preintervention need to show signs of decreased flow and preferably stasis with primary outflow through the recanalized iliac vein. If collateral outflow persists after common iliac vein stenting, this usually is a sign of inadequate stent extension caudally. The same applies in patients with endophlebectomy with or without AVF creation. Primary outflow should lead into the recanalized iliac tract, not retrograde into the femoral veins or collaterals. It is our conviction that this should also be treated with stent extension, if needed, across the inguinal ligament into the common femoral vein.

Follow-up imaging is primarily aimed at assessing stent and AVF patency, which is most easily done with duplex. Additionally we perform abdominal radiographs in four projections of the stented trajectory (Anterio-Posterior, lateral, left and right anterior oblique). These radiographs are to identify stent kinking, migration, fracture or changes in orientation. Only in selective cases additional imaging is required. Since haemodynamic information is crucial, the next step after duplex is conventional venography which allows us to not only visualize, but also treat any remaining stenosis or obstruction as well as complications in order to increase patency.

DISCUSSION

Although high grade evidence is still lacking in the emerging field of endovascular treatment of chronic venous obstructive disease, dedicated centres are quickly generating great amounts of clinical experience and more and more patients are treated for complex post-thrombotic aberrations. Iliofemoral obstructions reaching into the common femoral vein are of specific interest as endovascular treatment of the common femoral vein has not been well established, but intervention at the level of the common femoral vein is required to guarantee adequate inflow into to stented ilioacaval segments.

In this paper we describe our experience in assessing iliofemoral flow and indications for ancillary interventions combined with PTA and stenting by use of modern imaging modalities. It is noteworthy that even though techniques like DUS, MRV and IVUS can clearly show the intraluminal post-thrombotic aberrations, the actual aspect of the vein after venectomy with the naked eye is always worse than on imaging, stressing the need for surgical interventions in these patients (Figure 17). Safety and effectiveness of endophlebectomy and AVF in venous disease have been described in a small number of studies. Our own experience will be described elsewhere. As already mentioned Raju et al.¹⁹ described an endophlebectomy technique in 1999 in relation to axillary vein transfer for deep venous reflux correction in post-thrombotic limbs. They performed this operation in 83 limbs, in which the transplant patency rate was 83% after 10 years. They however did not specifically assess parameters of the endophlebectomy itself. Furthermore, their indications for treatment were based on severe PTS symptoms in the presence of venographic intraluminal post-thrombotic lesions, and treatment was aimed at deep venous reflux relief. And therefore the occlusive component of PTS in these patients was not addressed as it is done in current literature. Puggioni et al.¹⁰ described endophlebectomy of 23 vein segments in 13 patients in 2004. They did focus on the obstructive component of PTS, as indications were either to improve inflow into reconstructed vein segments, to allow for valve repair or to increase calf outflow. They reported a primary patency rate of 77% after a median of eight months. Lastly, Vogel et al.¹⁸ recently described endophlebectomy of the common femoral vein combined with PTA and stenting in 10 patients, of five of whom six-month follow-up data were available.

Figure 17. Surgical image showing the extensive intraluminal changes in the common femoral vein as a result of incomplete recanalization after a deep venous thrombosis more than one year ago. These changes correspond with the trabeculations visualized with magnetic resonance venography.

In two patients an adjunctive AVF was created. Patency was 80% at six months, and clinical scores (VCSS and Villalta) and quality of life all improved. Interestingly these authors noted that complications rates because of aggressive anticoagulation might have been reduced if AVFs were more frequently used instead. Despite these very favourable results it is important to realize that when combining endophlebectomy and AVF creation with PTA and stenting, outcome assessment is difficult as the individual contributions of these techniques to the final effect are intertwined. With regard to the technique it has not yet been established to what level the stents should be placed, specifically if there is a need to keep stents limited to the region cranial of the endophlebectomy, or to extend the stents into this region. And as new dedicated venous stents are now becoming available, the whole issue of femoral stenting might need to be revised.

Ideally we would like to have a parameter giving us the information in whom we should perform an endophlebectomy and/or an AVF creation to increase patency. To adequately address this still a lot of research has to be done and registries from all centers performing these procedures might give us more answers in the future.

CONCLUSION

Endovenous recanalization of post-thrombotic vein segments by PTA and stenting is a treatment quickly gaining popularity. Endovascular techniques suffice for ilio caval disease; however in case of femoral involvement adequate inflow from the common femoral vein into the iliac tract needs to be guaranteed. This can be done by performing an endophlebectomy and/or creating an AVF. Indications for these interventions are however at this moment not well established. In our experience careful preoperative assessment with DUS and MRV is needed and helpful. When intraluminal processes are present at the level of the common femoral vein below the SFJ the common femoral, femoral and deep femoral vein outflow are generally impaired, indicating the need for an additional surgical intervention.

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CHAPTER 7 ENDOPHLEBECTOMY OF THE COMMON FEMORAL VEIN AND ARTERIOVENOUS FISTULA CREATION AS ADJUNCTS TO VENOUS STENTING FOR POST-THROMBOTIC SYNDROME

M. A. F. de Wolf^{1,3}

H. Jalaie⁴

J. H. H. van Laanen¹

R. L. M. Kurstjens^{1,3}

M. J. S. Mensinck¹

M. J. de Geus¹

A. Gombert⁴

R. de Graaf²

C. H. A. Wittens^{1,3,4}

Departments of (1) Surgery and (2) Radiology, Maastricht University Medical Centre, and (3) Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands, and (4) Department of Vascular Surgery, University Hospital Rheinisch-Westfälische Technische Hochschule Aachen, Nordrhein-Westfalen, Aachen, Germany

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ABSTRACT

Background

Good results have been reported for angioplasty and stenting of post-thrombotic lesions of the iliac and proximal femoral veins. If lesions at the origin of the superficial femoral and profunda veins are stented, the intraluminal synechiae can be pushed against the orifices of inflow vessels, potentially decreasing stent inflow. Surgical disobliteration of the common femoral vein (endophlebectomy) has been suggested to mitigate this problem. Because of a temporary increase in thrombogenicity, this procedure may be accompanied by arteriovenous fistula creation.

Methods

Data on consecutive patients treated by hybrid venous reconstruction, between December 2010 and May 2015, were analysed. Standard recording consisted of clinical scoring systems (including Villalta scale) and imaging. Patency was assessed with duplex ultrasonography.

Results

Seventy-six legs (70 patients) were included. Median follow-up was 379 (range 73–1508) days. Primary, assisted primary and secondary patency rates at 12 months were 51, 70 and 83 % respectively. Sixty % of loss of primary patency (24 of 40 legs) was related to common femoral vein stenosis, and the rest to rethrombosis. Other complications included wound infection (29 %) and lymphatic leak (39 %). The Villalta score had decreased by a median of 7 points at 1-year follow-up.

Conclusions

The combination of venous stenting, endophlebectomy and arteriovenous fistula creation for patients with extensive post-thrombotic vein damage and severe post-thrombotic syndrome is feasible.

INTRODUCTION

During the past decade, percutaneous transluminal angioplasty (PTA) and stenting have become established treatments for chronic obstruction of the iliac and caval veins in a growing number of centres worldwide. This treatment for patients with post-thrombotic syndrome (PTS) is an alternative to symptom reduction by conservative compression treatment. In a number of patients, post-thrombotic damage extends below the level of the iliac veins. When treated by ilio caval venous stenting, these patients might be prone to increased risk of in-stent rethrombosis, because of decreased venous inflow from the damaged common femoral vein (CFV) and its inflow vessels. Stent extension below the inguinal ligament to the proximal femoral vein has been shown to be effective¹. In arterial stenting, stent extension into the common femoral artery is generally discouraged because of the fear of stent damage by movement of the hip joint, and hyperplasia². Hyperplasia, however, is not seen in venous stenting, but extending the stent to the distal CFV might hamper inflow from the superficial or deep femoral veins at the femoral confluence, as the synechiae are pushed into the vein wall and over sidebranch orifices. This might impair relief of symptoms and increase the risk of reocclusion.

It has been suggested that ilio caval stenting could be combined with surgical disobliteration of the CFV and the orifices of its side branches, which is termed endophlebectomy (or endovenectomy)^{3–6}. The advantage of combining iliac stenting with endophlebectomy is improved inflow into the stents by securing flow from all major side branches of the CFV, which should reduce the risk of rethrombosis. Moreover, it creates a single-lumen landing zone for the stent. However, the increased thrombogenicity resulting from surgical trauma by the endophlebectomy might cause early rethrombosis of the stents, CFV or both. In addition to a strict anticoagulation regimen, here endophlebectomy was combined with creation of a temporary arteriovenous fistula (AVF) to the CFV, to increase flow further through the treated venous tract.

The present study evaluated the feasibility, efficacy and safety of this hybrid venous recanalization procedure.

Methods

Between December 2010 and May 2015, consecutive patients with advanced venous disease (subjective complaints and/or objective skin changes) who had post-thrombotic damage affecting ilio caval veins extending into the CFV were considered for surgical treatment. The procedures were undertaken at Maastricht University Medical Centre and University Hospital Aachen. All follow-up was done in Maastricht.

Inclusion criteria

Age above 18 years and a life expectancy of at least 1 year. Significant venous disease defined as Clinical Etiologic Anatomic Pathophysiologic (CEAP) class C4–6; debilitating chronic pain or the presence of venous claudication⁷; post-thrombotic vein wall fibrosis and synechiae in at least the external iliac vein, and femoral or deep femoral vein, seen on duplex ultrasonography and magnetic resonance venography. Exclusion criteria were: unwillingness to receive or contraindications to prolonged anticoagulation treatment and recent deep vein thrombosis (DVT) within 1 year⁸.

Procedure

Access was obtained by ipsilateral ultrasound-guided puncture of the mid-thigh femoral vein. In a minority of patients a contralateral femoral vein or right jugular vein access was required. After gaining access, a small-calibre (5-Fr) sheath was positioned, and the exact anatomy was visualized by multiplane venography. After administration of 5000 units heparin, a hydrophilic coated guidewire and angulated catheter were used to recanalize the entire obstructed venous tract. Multiangle venography may be needed to check guidewire positioning, as collaterals can mimic the femoral, iliac or caval veins in size and location, especially on single-plane venography. Once recanalization of an unaffected vein cranially from the fibrosis (such as the vena cava) had been achieved, this guidewire was exchanged for a stiff guidewire. After securing successful recanalization, a longitudinal groin incision was made. The common femoral artery was dissected first, as it is easily identified and because it is needed as access for the arterial anastomosis of the AVF. After thrombosis, the inflammatory response is generally not restricted to scarring inside the femoral vein, but also the surrounding tissue, making the dissection significantly more difficult.

After the CFV and all its side branches had been dissected and controlled with vessel loops, an 8–10-cm longitudinal venotomy of the CFV was made, starting just above the origin of the great saphenous vein to the femoral confluence (Figure 18A). Because there is no natural dissection plane, the intraluminal synechiae had to be removed by sharp dissection. Care was taken to preserve the remaining thin wall of the CFV and avoid perforation (Figure 18B). Venous inflow from all side branches was achieved by the endophlebectomy as far into the orifice as possible and mechanical dilatation beyond, using a smooth clamp, to ensure good inflow. Depending on vessel diameter, the venotomy was closed primarily or with a bovine patch. Next, a 6-mm externally supported polytetrafluoroethylene (PTFE) vascular graft was used to create an AVF between the common femoral artery and CFV. The venous anastomosis of the fistula was created at the cranial or caudal side of the venotomy and venous flow was restored⁹. The vascular graft was cut to length, about 60 mm, and the fistula was given a loop-like shape to simplify later percutaneous plug occlusion (Figure 18C). The arterial anastomosis was then created and fistula flow released and checked. The venotomy was marked cranially by two surgical clips to determine the exact distal stent position

later on during fluoroscopy. After meticulous haemostasis (because the patient was fully anticoagulated), the groin incision was closed with a small drain.

Figure 18. Intraoperative images of endophlebectomy. a Intraluminal post-thrombotic scarring can be identified obstructing the common femoral vein (CFV). Vessel loops are seen controlling the major and minor side branches of the CFV. b After endophlebectomy the majority of fibrotic tissue is removed. The guidewire can be seen intraluminally. c The externally supported polytetrafluoroethylene (PTFE) graft can be seen connecting the common femoral artery and CFF.

PTA of the iliofemoral tract was then performed with non-compliant balloons sizes 16 to 12 mm (12-mm Powerflex[®] and 16-mm Maxi[®] LD, Cordis, Johnson & Johnson, Diegem, Belgium; 14-mm Armada[®], Abbott, North Chicago, Illinois, USA). PTA was followed by stent placement (sinus-XL, sinus-Venous and sinus-XL Flex, Optimed, Ettlingen, Germany; Zilver Vena[™], Cook, Galway, Ireland), cranially extending to the inferior vena cava. The caudal landing zone of the stent was just cranial to the venous anastomosis of the PTFE, as marked by the surgical clips. Stents were postdilated and venous flow was checked by multiplane venography (Figure 19). Some patients with bilateral iliac and caval treatment had the confluence reconstructed with balloon-expandable stents (AndraStent[®]; Andramed, Reutlingen, Germany)¹⁰. Antibiotic prophylaxis or an antibiotic-coated sponge was used according to hospital protocol and the surgeon's judgement.

Postoperative care

Intermittent pneumatic compression of the legs was started after operation in all patients and continued during the hospital stay. In patients already on oral anticoagulation, this was not stopped before surgery and was continued after operation, aiming at an international normalized ratio (INR) of 3–4. In all others, low molecular weight heparin was started directly after the intervention; coumadins were started the next day, if no active bleeding was present, aiming at an INR of 3–4. Anticoagulation was continued for at least 6 months.

Figure 19. Perioperative venography. a Obstruction of left common and external iliac vein, and common femoral vein (CFV). Multiple collateral veins cross the midline. b Stent in left common and external iliac vein, and CFV. c Close-up of distal stent and vascular clips (arrow) marking the proximal endophlebectomy. d Diagram of stents, endophlebectomy of CVF and arteriovenous fistula

If no stenoses were found on duplex examination 2–3 weeks after surgery, patients were booked for a second hospital admission, during which the AVF was closed. If a stenosis in the endophlebectomy segment was identified, impairing outflow of the leg and reducing inflow into the stented segment, stent extension was performed before the AVF was closed. AVFs were closed in an endovascular procedure using an Amplatzer™ vascular plug (St Jude Medical, St Paul, Minnesota, USA) via contralateral transfemoral arterial access. A small number of AVFs were closed surgically.

Data collection

From 2012 onwards, data were added to a prospective digital database. Data collected before this time point were added retrospectively (4 patients). During follow-up, C of CEAP, Venous Clinical Severity Score (VCSS), Villalta score, venous claudication and the presence of any pubic collateralization were noted^{7,11,12}. Some of these data were not documented in the interval before the digital database.

Statistical analysis

Continuous data are presented as median (range), and categorical data as frequencies and percentages. The t-test was used to analyse changes in clinical scores. Patency was defined as less than 50 % flow lumen reduction in a treated vein segment. Patency rates were estimated by use of Kaplan–Meier survival analyses, based on the total number of legs that received endophlebectomy and AVF. All other data are based on the number of patients. $\alpha \leq .050$ was used to demonstrate statistical significance.

RESULTS

A total of 70 patients (76 legs) were treated. Median age was 39 (18–75) years and 44 patients (63 %) were women. All patients had extensive post-thrombotic damage on imaging, and all but one patient reported one (47 patients, 67 %) or more (22 patients, 31 %) DVTs in their medical history. One patient had a silent DVT. Patients were treated a median of 5 (1–41) years after the first DVT. The ipsilateral common iliac vein was affected in 64 patients (91 %) and the external iliac vein in all patients, as was the CFV. The CFV was affected by post-thrombotic disease in 66 patients (94 %), and the deep femoral vein in 55 (79 %). Other baseline data can be found in Table 13.

Intervention

Fifty-five patients (79 %) had unilateral treatment and in six (9 %) the operation was performed bilaterally (in 4 (6 %) the vena cava was also stented). Nine patients (13 %) had bilateral stenting (in 8 (11 %) the vena cava was also stented), in combination with unilateral endophlebectomy and AVF creation. Thus, 76 endophlebectomies and AVFs were created. In 37 patients (53 %) a patch was used to close the venotomy; it was closed primarily in the other 33 patients.

Table 13. Demographics

	Baseline (N=70)	Percentage	Range
Number of females	44	62,9%	
Median age (years)	39		18 - 75
Median BMI	27.0		21.8 - 32.8
Thrombophilia	20*	76,9 %	
Single DVT	47	67,1%	
Recurrent DVT	22	31,4%	
Median time between DVT and treatment (years)	5		1- 41
Left sided DVT	41	58,6%	
Right sided DVT	2	2,9%	
Bilateral DVT	27	38,6%	
History of PE	11	15,7%	
Highest C of CEAP			
C0	6	8,6%	
C1	5	7,1%	
C2	8	11,4%	
C3	31	44,3%	
C4a	11	15,7%	
C4b	3	4,3%	
C5	3	4,3%	
C6	3	4,3%	
Mean VCSS at baseline	8		3 - 19
Mean Villalta score at baseline	11		4 - 22
Venous claudication at baseline	64	91,4%	

*28 (40%) of patients tested for thrombophilia

In unilateral hybrid reconstructions, a median of 2 (1–6) stents were used. In patients with stenting of the vena cava and the bilateral iliofemoral tract, with either unilateral or bilateral endophlebectomy, a median of 6 (5–9) stents were used. In the three patients with bilateral treatment without stenting of the vena cava a total of four stents were used per patient. AVFs were closed by endovascular means in 28 patients (40 %) and surgically in four (6 %). In 15 individuals (21 %) the AVF closed spontaneously, and in 23 (33 %) the AVF was not closed during follow-up, because inflow from the femoral and/or deep femoral vein was judged to be inadequate. If the AVF was closed, this was done a median of 82 (26–742) days after its creation.

Patency rates and reinterventions

Median follow-up was 379 (73–1508) days. The patency rate at 12 months was 51,70 and 83 % respectively for primary, assisted primary and secondary patency (Figure 20). In patients who received bilateral stenting with unilateral endophlebectomy and AVF creation,

nine of the ten iliofemoral tracts treated by sole stenting (without endophlebectomy and AVF) remained patent during follow-up. In total, 40 limbs lost primary patency in 39 patients (56 %) (53 % of treated limbs). This was due to reocclusion in 16 patients (23 %); half of these occurred before AVF closure. Reocclusion was treated by catheter-directed ultrasound-enhanced thrombolysis in seven patients (10 %), and was successful in five. Three of the five patients who had successful thrombolysis needed restenting because of inadequate inflow. In nine patients (13 %) thrombolysis or thrombectomy was not considered, either because of an absolute contraindication or because the treatment window had passed. The most frequently performed reintervention was restenting, that is elongation of the stented tract into the endophlebectomy zone, because of restenosis of the CFV. This was necessary in 24 patients (34 %) and was performed with the same self-expandable stents as used for primary stenting. In another eight patients (11 %) stenosis of the CFV occurred during follow-up, and a wait-and-see approach was chosen, generally because the stenosis was asymptomatic.

Figure 20. Kaplan–Meier analysis of primary, assisted primary and secondary patency rates of vein segments treated by the hybrid intervention, calculated per leg.

Error bars represent standard error of the mean (all less than 10 %)

Other complications

Besides reocclusion and CFV stenosis, the most frequent complications related to the groin incision. Twenty patients (29 %) developed wound infections. Surgical incision and drainage was necessary in seven patients (10 %), intravenous antibiotics were used in 11 (16 %) and oral antibiotics in all. The PTFE AVF had to be removed because of persistent infection in two patients (3 %), in both of whom the AVF was already occluded. Twenty-seven patients (39 %) developed a lymphatic leak after surgery, which was managed by

negative-pressure wound therapy in six (9 %) and by conservative measures in the rest. Other important complications included major bleeding (needing transfusion and/or surgical intervention) in six patients (9 %) (Table 14).

Table 14. Complications

Complications		Percentage
Reocclusion	16	25
Pulmonary embolism	0	0
Stenosis distal to stents	32	46
Wound infection	20	31
Lymphorrhea	26	40
Minor bleeding	11	17
Major bleeding	6	9
Neuropraxia	2	3
Heparin induced thrombocytopenia	1	2
Bladder infection	1	2
Mild stent tapering (not needing re-intervention)	7	11
Stent kinking	2	3
Residual stent compression	2	1
Proximal stent placed too distally	2	3
Stent fracture	0	0

Clinical follow-up

Follow-up data were available for 67 patients (96 %) at 6 months and 40 (57 %) at 12 months. Median VCSS decreased from 8 (3–19) at baseline to 6 (0–21) at 6 months and 5 (0–21) at 12-month follow-up ($P < 0.001$, baseline versus 12 months). Median Villalta score decreased from 11 (4–22) at baseline to 5 (0–15) at 6 months and 4 (0–21) at 12 months ($P < 0.001$, baseline versus 12 months). Based on the categorical Villalta scale (no, mild, moderate or severe PTS) in the 40 patients who completed 1-year follow-up, 28 patients improved on this scale, 11 were unchanged and one had worse symptoms. Among the 64 patients with venous claudication at baseline, this disappeared in 46 (72 %). Two of the patients with active ulcers suffered an early reocclusion (at 43 and 98 days after operation), and the ulcers did not heal during follow-up. A third patient had an ulcer that healed 25 days after the intervention, without recurrence.

Discussion

This study reports an experience with the use of a hybrid venous reconstruction for PTS: stenting of the (cavo)iliofemoral tract combined with endophlebectomy and AVF creation. Interest in this technique arose some years ago^{5,6,9,13–15}, but outcome data are still sparse. Clinical results reported here at mid-term follow-up are favourable, especially considering the extent of the post-thrombotic venous changes. However, the primary patency rate of 51 % at 1 year is significantly lower than that after sole iliofemoral

vein stenting, which is generally reported as being 70–80 %^{16–18}. Assisted primary and secondary patency rates are little different from those after sole iliofemoral stenting.

The technique described suffers from the inherent thrombogenicity of the extensive stenting, but also of the surgically exposed vein wall components (collagen). This is the reason for creating an AVF in all these patients, a decision based on the now infrequently performed surgical thrombectomy for DVT¹⁹. The proportion of patients (46 %) who developed a stenosis of the CFV during follow-up is of note. This area was free from stenosis at the end of the operation, as checked by completion venography, so the stenoses must have developed during follow-up. Stenosis may be caused by low intravenous pressure and possible compression by fluid extravasation around the endophlebectomy tract. This might be preventable by insertion of an inlay stent. The AVF may also influence this problem, possibly because of its interaction with the newly endophlebectomized CFV or the stents. The role of AVFs in creating venous obstruction, due to intimal hyperplasia, is well known in vascular access surgery^{9,20}, which is why temporary AVFs were used here.

In comparison with other published series of ilio caval venous stenting, the present patency rates fall between the ranges of Garg and colleagues²¹, with a primary patency rate of 8 % and secondary patency rate of 30 %, and Vogel et al.⁴ and Puggioni and coworkers⁵, who reported primary patency rates of around 80 % and secondary patency rates of around 90 %. Because of the groin incision many wound complications are noted, especially lymphatic leak and wound infection, which significantly influence the early postoperative phase for these patients. Limitations of this study include the fact that data were partly collected retrospectively (4 patients) and not all patients completed 12-month follow-up. Moreover, a learning curve effect may be present as this series also represents an early experience. However, the intervention and follow-up were standardized, and patency rates and objective clinical scores were both collected.

CONCLUSION

The combination of venous stenting, endophlebectomy and AVF creation for patients with extensive post-thrombotic vein damage causing severe PTS is feasible. Clinical scores improve significantly. Patency rates are suboptimal but acceptable in this population with extensive post-thrombotic damage, and an alternative to the standard compression treatment.

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CHAPTER 8

RECONSTRUCTION OF THE FEMORO-ILIO-CAVAL OUTFLOW BY PERCUTANEOUS AND HYBRID INTERVENTIONS IN SYMPTOMATIC DEEP VENOUS OBSTRUCTION

T.M.A.J. van Vuuren^{1,2}

M.A.F. de Wolf^{1,2}

C.W.K.P. Arnoldussen^{3,4}

R.L.M. Kurstjens^{1,2}

J.H.H. van Laanen¹

H. Jalaie⁵

R. de Graaf³

C.H.A. Wittens^{1,2,5}

1 Department of Surgery, Maastricht University Medical Centre, P. Debyelaan 25, 6202 AZ, Maastricht, The Netherlands

2 Cardiovascular Research Institute Maastricht, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands

3 Department of Radiology, Maastricht University Medical Centre, P. Debyelaan 25, 6202 AZ, Maastricht, The Netherlands

4 Department of Radiology, VieCuri Medical Centre, Venlo, The Netherlands

5 Department of Vascular Surgery, University Hospital RWTH Aachen, Nordrhein-Westfalen, Pauwelsstraße 30, 52074, Aachen, Germany

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ABSTRACT

Objective/Background

Deep venous obstruction is relatively prevalent in patients with chronic venous disease. Endovascular treatments and hybrid interventions can be used to relieve venous outflow obstructions. This paper assesses mid-term clinical outcomes and patency rates in a large cohort after percutaneous and hybrid interventions.

Methods

This was a prospectively analysed cohort study. Patients with symptomatic deep venous obstruction who presented at a tertiary referral hospital were divided into three groups: patients who underwent percutaneous stenting for non-thrombotic iliac vein compression syndrome (IVCS group); patients with post-thrombotic syndrome (PTS) treated by percutaneous stent placement (P-PTS group); and PTS patients with obstruction involving the veins below the saphenofemoral junction in which a hybrid procedure was performed, combining stenting with open surgical disobliteration (H-PTS group). Patency rates, complications, and clinical outcomes were analysed.

Results

A total of 425 lower extremities in 369 patients were treated. At 60 months, primary patency, assisted primary patency, and secondary patency rates were 90%, 100%, and 100% for IVCS, and 64%, 81%, and 89% for the P-PTS group, respectively. The H-PTS group, showed patency rates of 37%, 62%, and 72%, respectively, at 36 months. Venous claudication subsided in 90%, 82%, and 83%, respectively. At the 24 month follow-up, mean Venous Clinical Severity Score decreased for all patients and improvement in Villalta score was seen in post-thrombotic patients. The number of complications was related to the extent of deep venous obstruction in which patients in the H-PTS group showed the highest complication rates (81%) and re-interventions (59%).

Conclusion

Percutaneous stent placement to treat non-thrombotic iliac vein lesions, and post-thrombotic iliofemoral obstructions are safe, effective, and showed patency rates comparable with previous research. Patients with advanced disease needing a hybrid procedure showed a lower patency rate and more complications. However, when successful, the clinical outcome was favourable at mid-term follow-up and the procedure may be offered to selected patients.

INTRODUCTION

Minimally invasive endoluminal interventions have revolutionised many facets of modern medicine. Since the 1990s great advances have been made in the treatment of iliac and vena cava obstructions where endovascular treatment options frequently surpass conservative therapy and open surgery.¹⁻⁵ Caval and iliofemoral venous obstructive disease is common in patients with chronic venous insufficiency and is caused by either post-thrombotic vein damage, extraluminal vein compression, or a combination of both. This post-thrombotic vein damage with vein wall fibrosis, intraluminal scarification, and valvular damage can result after a deep venous thrombosis (DVT), presenting as the so called post-thrombotic syndrome (PTS).^{6,7} Clinically, this is associated with the same symptoms and clinical signs as other types of chronic venous disease, for example pain (especially during ambulation), oedema, and venous ulceration.

As mentioned, the second most common cause of chronic venous obstruction is related to extraluminal vein compression of which iliac vein compression syndromes (IVCS) are the best known. IVCS consist of symptoms associated with chronic venous disease due to compression of the iliac vein by an extraluminal structure (usually an overlying artery).⁸ Additionally, there can be some degree of spurs or webs due to chronic local vein wall irritation in about 30% of cases.^{9,10} In this subgroup, a smooth vessel wall and focal indentation will be seen during recanalisation, indicating compression without post thrombotic vein damage.¹¹ Both the post-thrombotic and IVCS obstruction impede ambulatory venous outflow of the lower extremity and lead to venous hypertension. Venous outflow of the leg seems most dependent on the iliac tract, which explains the significantly higher incidence of PTS after an iliofemoral DVT when compared with calf level DVTs.^{6,12} PTA and stenting of iliac lesions have been shown to improve outflow of affected legs.^{1e4} Moreover, stenting is performed and has been proven to be more effective in patients with a common femoral vein (CFV), external iliac vein, common iliac vein (CIV), or inferior vena cava (IVC) obstruction.^{2e4} Because stenting distal to the CFV has a higher risk of early failure due to low flow, this is generally not offered and is avoided.^{1,13e15} In addition, there is currently no evidence suggesting any clinical benefit from stenting below the common femoral confluence, which is where the deep femoral vein (DFV) and femoral vein (FV) merge into the CFV. However, open surgical disobliteration, may be a solution for selected patients with post-thrombotic changes at and below the CFV.¹⁶⁻¹⁸ The goal of this study is to report on the experience, clinical outcome, and stent patency in patients treated for IVCS and post-thrombotic femoral, iliac, and caval obstructive lesions by percutaneous and hybrid techniques.

Methods

In this cohort study data were collected prospectively and analysed retrospectively. All patients eligible for treatment at the authors' tertiary referral care centre (vascular surgery department) were included. Between September 2009 and January 2016, 369

consecutive patients were treated. All patients showed signs of chronic caval, iliac, or femoral vein obstruction on diagnostic imaging and demonstrated symptoms of venous hypertension like pain interfering with daily activities, and/or clinical signs classified according to the CEAP classification as C₃ (edema) or C₄-C₆ (skin changes).¹⁹ Additionally, venous claudication was a symptom indicating treatment and was defined as the onset or worsening of pain during routine exercise, which subsides during rest, especially while sitting or lying down.¹⁴

Patients who received stents after catheter directed thrombolysis for an acute DVT were excluded from this study. Non-fully grown adolescents (bone age analysed if applicable) with a DVT < 1 year previously, and patients with a life expectancy of < 1 year were not eligible for treatment. Also, patients with an occlusion extending far into the FV and DFV were not eligible for treatment as it is impossible to reestablish the inflow to the stent. Furthermore, treatment was not offered to those patients who were intolerant of anticoagulant therapy since this was obligatory after the intervention. Patients had magnetic resonance venography (MRV) and duplex ultrasonography (DUS) imaging at baseline, and conventional multiplanar venography during intervention. IVCS was defined as clinical complaints related to a > 50% lumen diameter reduction on DUS or MRV in combination with compression and a collateral network on venography. Intraluminal synechiae outside the compressed segment, with formation of collaterals, was considered a sign of post-thrombotic obstruction.

On the basis of findings, three groups were created in which interventions were performed. The IVCS patients with non-thrombotic syndrome had percutaneous stent placement alone. Percutaneous stent placement (P-PTS group) patients, had a percutaneous stent placement when obstruction was limited to segments central to the saphenofemoral junction (SFJ) in the CFV or when a trabeculation free landing zone in the CFV between the SFJ and the DFV and FV confluence was identified. The inflow from the FV, DFV, and/or collaterals was minimally impaired. The third group (H-PTS) consisted of patients with PTS and obstruction below the SFJ, especially when the CFV was occluded or when there was a risk that stent placement could displace intraluminal tissue and obstruct FV or DFV inflow. Also, when the orifices of the FV and/or the DFV were occluded patients were included in the H-PTS group. Furthermore, endophlebectomy and arteriovenous fistulae (AVF) were performed as a second stage in some patients treated in the P-PTS group with stent thrombosis and clinical complaints interfering with daily activities. Clinical scores, stent patency rates, complication rates, and number of reinterventions are presented per leg for all three groups.

Clinical assessment pre-intervention

At baseline, CEAP classification and the Venous Clinical Severity Score (VCSS) were scored for all patients. PTS was diagnosed using the Villalta score. With increasing

clinical experience, the importance of venous claudication was recognised and a separate scoring for this item was added to the baseline and follow-up data collection. For this reason, not all venous claudication scores were present at baseline. The number of entered data is described in the text. Consequently, scores were inconsistently entered into a digital database at the various follow-up visits and at the discretion of the treating physician.

Duplex ultrasonography

DUS (MyLab Alpha, Esaote, Genoa, Italy; ProSound Alpha 7 Premier machine, Hitachi Aloka, Tokyo, Japan) at baseline included imaging of the IVC from the level of the liver downward, the renal and gonadal veins, the iliac veins, and any apparent collateral network in the supine position using a convex probe (frequency range 1e8 MHz). Special attention was given to any clues of post-thrombotic damage or IVCS, that is, venous stenosis, external vein compression, vessel wall changes, intraluminal scarification, and enlarged collateral veins. With the patient in an erect position, the femoral, popliteal, and calf veins were examined using a linear array probe (frequency range 3e13 MHz). Inflow of the FV, DFV, and GSV into the CFV was evaluated during flow augmentation. Furthermore, the superficial and deep veins were tested for valvular segmental reflux. Insufficiency was scored as retrograde flow > 1 s for the deep veins and > 0.5 s for the superficial veins.

Magnetic resonance venography

A 1.5-Tesla MRI system (Intera, Philips Healthcare, Best, the Netherlands) was used. A dedicated 12 element phased array peripheral vascular coil with craniocaudal coverage of 128 cm (Philips) was used for signal reception. Examinations were performed in the supine position. Prior to contrast injection, all patients had a standard two dimensional non-contrast enhanced balanced turbo field echo (BTFE) sequence to visualise the abdominal and pelvic veins. By use of a remote controlled dual head injector (Spectris; Bayer Medrad, Indianola, PA, USA) the contrast agent (Gadobutrol; Gadavist, Bayer HealthCare, Berlin, Germany) was administered intravenously at 1.0 mL/second (0.2 mL per kg body weight, equal to 0.2 mmol/kg) in the median cubital vein. Contrast injection was followed by a 20 mL saline flush injection at the same flow rate. Acquisition of the first scan volume was started 30 s after contrast administration. A three dimensional ultrafast gradient echo sequence (Ultrafast GE, THRIVE, Philips Healthcare) with fat suppression (spectral presaturation with inversion recovery) was used for high resolution steady state imaging of the venous system, ensuring coverage of the popliteal veins up to the suprarenal IVC.

Stent placement

Endovascular interventions were performed in an angiosuite, whereas hybrid procedures were performed in a hybrid operation room. Ultrasound guided venous access was obtained through the ipsilateral midfemoral vein, below the inflow of the

main deep femoral vein branches. In general, a 6-F sheath was introduced to initiate recanalisation. After successfully traversing the guidewire through the obstruction, the 6-F sheath was changed for a 10-F sheath to facilitate balloon angioplasty and stent deployment. Routinely, 5000 IU of heparin were administered before angioplasty. Predilatation was performed in which balloons were sized according to the diameter of the desired stent, generally between 12 and 16 mm, increasing from the CFV to the CIV, and up to 25 mm for the IVC. The type of stents used varied during the course of the study, on the basis of experience. Without specific indication, stents used included the sinus XL, sinus XL-flex, sinus Venous and sinus Obliquus (Optimed GmbH, Ettlingen, Germany), VICI (Veniti, St. Louis, MO, USA), Zilver Vena (Cook, Limerick, Ireland), and Venovo (Bard, Coving-ton, GA, USA). Postdilatation was always performed. Detailed descriptions of the recanalisation and stenting techniques are described elsewhere.^{14,15,20} Poststenting assessment of the in- and outflow of the treated segments was routinely done by multiplanar venography (Figure 21).

Figure 21. (A) Preinterventional venography of the left iliac tract in a patient with post-thrombotic syndrome who received percutaneous treatment. The proximal iliac tract is not visualised because of lumen occlusion. Multiple collaterals are seen; a secondary sign of vein obstruction. (B) Roadmap image following guidewire recanalisation and percutaneous transluminal angiography of the left iliac tract. Notice the typical translucency in the common iliac vein caused by the compression of the overlying common iliac artery. (C) Venography after stent deployment. Contrast flows freely through the stents. (D) Fluoroscopic image of the stents post-deployment. Stents reach from the proximal common iliac vein into the proximal common femoral vein.

During follow-up, the same DUS techniques as pre-intervention were used, with specific attention to stent and, if applicable, AVF patency, presence of lumen diameter

reduction of > 50%, presence of post-interventional haematomas, and stent integrity. Features such as stent fracture, kinking, or tapering resulting in lumen reduction and apparent flow impairment were recorded. A suspicion of kinking was scored as any in-stent angulation causing flow impairment, most frequently caused by rigidity of the stent. When the suspicion of kinking arose, a plain X-ray in three planes was performed. Tapering was scored as an indentation at the stent end due to external compression, causing flow impairment with filling of collaterals.

Analysis and statistics

All continuous data are presented as mean SD, except for non-normally distributed data (presented as median [range]). Categorical data are presented as frequencies and percentages. An α of .05 was considered statistically significant. KaplanMeier survival estimation was used to calculate patency rates. SEM values of > 10% were discarded as being unreliable and were not reported. Patency analyses were based on the total number of extremities treated, whereas all other calculations were per patient. Clinical scoring data were absent after 24 month follow-up, as these data were available in < 20% of patients. A clinically relevant difference of minimally 0.5 times the SD of the difference in pre- and post-treatment scores was used as a cutoff value (of 210 [57%] patients with both a baseline and at least one follow-up score). The study was registered under number NCT02650453 in the clinicaltrials.gov database.

RESULTS

Demographics

The mean age of the total population was 43 ± 14 years (range 17-77 years) and 257 (70%) patients were female. Most (261 [93%]) patients in the P-PTS and H-PTS groups had one or more known DVTs in their medical history. Twenty-one patients (6%) referred for analysis of chronic venous disease had suffered an occult DVT with post-thrombotic vein damage. Patients in the P-PTS and H-PTS groups had a median of 6 (range 1-48) symptomatic years after their first DVT. A minority of IVCS patients was also known to have a history of DVT; however, these were distal or contralateral DVTs. The majority (242 [66%]) of patients were classified as CEAP class Co-C3. Treatment indication in these patients was based on the presence of venous claudication and other subjective complaints like pain or oedema. At baseline, venous claudication was present in 33 patients with IVCS (of 83 patients in whom claudication was noted at baseline), 113 P-PTS patients (of 181 patients in whom claudication was noted at baseline) and 70 H-PTS patients (of 83 patients of whom claudication was noted at baseline). All patient characteristics are provided per group in Tables 15 and 16.

Table 15. Demographics

	IVCS N= 87 (24)	P-PTS N=196 (53)	H-PTS N= 86 (23)	Total N=369
N legs*	87 (21)	221 (53)	109 (26)	417
Number of females	74 (85)	127 (65)	56 (65)	257 (70)
Mean age $\pm$ SD (y)	43 $\pm$ 13	45 $\pm$ 13	40 $\pm$ 15	43 $\pm$ 14
Single DVT	18 (21)	133 (68)	53 (62)	204 (55)
Recurrent DVT	6 (7)	44 (22)	31 (36)	81 (22)
Silent DVT	N.A.	19 (10)	2 (2)	21 (6)
History of PE	5 (6)	31 (16)	13 (15)	49 (13)
Median time between DVT and treatment (y)	N.A.	7 (1-48)	5 (1-40)	6 (1-48)

Note: Data are n (% of subgroup) unless otherwise indicated. IVCS= iliac vein compression syndrome, P-PTS= post-thrombotic syndrome with percutaneous treatment, H-PTS= post-thrombotic syndrome with hybrid treatment P-PTS= percutaneous post thrombotic syndrome, H-PTS= hybrid post thrombotic syndrome

* indicates percentage of total number of legs.

Y= years; DVT= deep venous thrombosis; N.A.= not applicable; PE= pulmonary embolism

Table 16. CEAP classification and reflux

	IVCS N= 87 (24)	P-PTS N=196 (53)	H-PTS N= 86 (23)	Total N=369
N of patients with CEAP	84 (97)	184 (94)	83 (97)	351 (95.)
C-class 0	5 (6)	16 (9)	7 (8)	28 (8)
C-class 1	10 (12)	16 (9)	9 (11)	35 (10)
C-class 2	20 (24)	22 (12)	10 (12)	52 (14)
C-class 3	36 (43)	60 (33)	31 (37)	127 (34)
C-class 4a	6 (7)	33 (18)	15 (18)	54 (15)
C-class 4b	2 (2)	8 (4)	4 (5)	14 (4)
C-class 5	2 (2)	12 (7)	3 (4)	17 (5)
C-class 6	4 (5)	15 (8)	4 (5)	23 (6)
Superficial venous reflux	45 (52)	72 (37)	12 (14)	129 (35)
Deep venous reflux	12 (14)	53 (27)	15 (17)	80 (22)
Perforator vein reflux	31 (36)	17 (9)	12 (14)	60 (4)

Note: Data are n (%) unless otherwise indicated. IVCS= iliac vein compression syndrome, P-PTS= post-thrombotic syndrome with percutaneous treatment, H-PTS= post-thrombotic syndrome with hybrid treatment PTS= percutaneous post thrombotic syndrome, H-PTS= hybrid post thrombotic syndrome

Intervention

In 284 (77%) patients, a left sided intervention was performed, 29 (8%) had a right sided and 52 (14%) had bilateral intervention. An isolated IVC treatment was performed in four (1%) patients. Thus, a total of 425 lower extremities were treated. Unilateral disease was treated with a median number of two (range 1-5) stents per patient and a median of five (range 2-8) for bilateral cases. In the H-PTS group 80 (93%) patients received stenting in combination with endophlebectomy and an AVF. Seven of those 80 patients had a bilateral endophlebectomy and AVF. Four patients were stented with an endophlebectomy without an AVF and two patients received stenting with an AVF but without an endophlebectomy. A bovine patch was used when closing the venotomy in 42 (49%) patients.

Patency rates and reinterventions

Primary patency rates at the 60 month follow-up were 90% and 64% for the IVCS and P-PTS groups, respectively. Assisted primary patency rates were 100% and 81%, and secondary patency rates 100% and 89%, respectively. The H-PTS group had a shorter follow-up of 36 months showing a primary, assisted primary, and secondary patency rate of 37%, 62%, and 72%, respectively. Patency rates are shown in Figure 22.

Figure 22. Cumulative patency rates of stented limbs in the total population, and of the iliac vein compression syndrome (IVCS), percutaneous post-thrombotic syndrome (P-PTS) and post-thrombotic syndrome with hybrid treatment (H-PTS; definitions explained in text) subgroups. The number at risk at each interval is given below the graph. All SEM are < 10%. (A) Patency rates of the total population. (B) Patency rates of the IVCS subpopulation. (C) Patency rates of the P-PTS subpopulation. (D) Patency rates of the H-PTS subpopulation.

In the IVCS group there were no thrombotic stent occlusions. Primary patency loss was due to reinterventions of persistent stenoses. In the P-PTS population 36 (18%) patients had a thrombotic stent occlusion. These thrombotic stent occlusions were treated by thrombolysis with secondary stenting in 19 patients, of whom two received thrombolysis twice and two required a thrombectomy. The remaining 15 thrombotic stent occlusions did not induce severe complaints interfering with daily activities and therefore did not receive an additional intervention. In the H-PTS group 33 (38%) patients suffered a thrombotic stent occlusion, of whom 10 (12%) received thrombolysis. Sixteen cases (8%) in the P-PTS group and 10 cases (12%) in the H-PTS group required a secondary open surgical procedure (revision or additional endophlebectomy and/or AVF) to optimise inflow into the stents. Restenting for new or previously unrecognised lesions, residual compression, or stent related issues was performed in seven (8%), 49 (25%), and 46 (53%) cases in the IVCS, P-PTS, and H-PTS groups, respectively (Table 17).

Table 17. Number of reinterventions per patient

	IVCS N= 87 (24)	P-PTS N=196 (53)	H-PTS N= 86 (23)	Total N=369
None	80 (92)	144 (74)	35 (41)	259 (70)
> 1 reintervention	0 (0)	22 (11)	19 (22)	41 (11)
Only PTA	0 (0)	11 (6)	10 (12)	21 (6)
CD-Thrombolysis	0 (0)	21 (11)	10 (12)	31 (8)
Thrombectomy	0 (0)	2 (1)	3 (4)	5 (1)
Restenting	7 (8)	38 (19)	42 (49)	87 (24)
Restenting + thrombectomy	0 (0)	3 (2)	2 (2)	5 (1)
Restenting + AVF	0 (0)	1 (1)	1 (1)	2 (1)
Restenting + endophlebectomy + AVF	0 (0)	7 (4)	0 (0)	7 (2)
AVF + endophlebectomy + restenting after hybrid procedure	0 (0)	0 (0)	1 (1)	1 (<1)
Endophlebectomy	0 (0)	0 (0)	1 (1)	1 (<1)
Creating AVF	0 (0)	4 (2)	1 (1)	5 (1)
AVF + thrombectomy	0 (0)	2 (1)	0 (0)	2 (1)
AVF + endoflebectomy + bypass	0 (0)	2 (1)	0 (0)	2 (1)
Revision AVF + Thrombectomy	N.A.	N.A.	6 (7)	6 (2)
Excision PTFE AVF	N.A.	2 (1)	4 (4)	6 (2)
Transposition	0 (0)	2 (1)	2 (2)	4 (1)
Bypass	0 (0)	0 (0)	1 (1)	1 (<1)

Note. Data are n (% of subgroup) unless otherwise indicated. IVCS = iliac vein compression syndrome; P-PTS = post-thrombotic syndrome with percutaneous treatment; H-PTS = post-thrombotic syndrome with hybrid treatment; PTA = percutaneous transluminal angioplasty; CD = catheter directed; AVF = arteriovenous fistula; NA = not applicable; PTFE = polytetrafluoroethylene.

All in all, the majority of patients who were treated in a hybrid fashion needed at least one reintervention (59%) versus 27% in the P-PTS and 8% in the IVCS groups. In addition, they needed the first reinterventions earlier after their primary intervention compared with the IVCS group. The median number of days between the first and second intervention in the IVCS group was 143 days (range 20-300 days) versus 140 days (range 17-355 days) in the P-PTS group and 48 days (range 11-115 days) for the H-PTS group.

Other complications

The most frequent complications were thrombotic stent occlusion and restenosis (Table 18). Contralateral DVT was rare and only seen in two patients (1%). Mortality was zero and there were no instances of clinical pulmonary embolism.

Table 18. Complications per patient

	IVCS N= 87 (24)	P-PTS N=196 (53)	H-PTS N= 86 (23)	Total N=369
None	63 (73)	98 (50)	25 (29)	186 (50)
Thrombotic stent occlusion	0 (0)	36 (18)	33 (38)	69 (19)
Stent stenosis	2 (2)	30 (15)	24 (28)	56 (15)
Residual stent compression	16 (18)	14 (7)	4 (5)	34 (9)
Minor bleeding	2 (2)	16 (8)	14 (16)	32 (9)
Major bleeding	0 (0)	2 (1)	11 (13)	13 (4)
Aneurysma spurium	1 (1)	0 (0)	1 (1)	2 (1)
DVT distally of stents	0 (0)	1 (1)	3 (4)	4 (1)
Contralateral DVT	0 (0)	1 (1)	1 (1)	2 (1)
Thrombophlebitis	1 (1)	2 (1)	0 (0)	3 (1)
Anaphylactoid reaction to contrast	0 (0)	0 (0)	0 (0)	1 (<1)
Non-specific				
Urinary tract infection	0 (0)	2 (1)	0 (0)	2 (1)
Priapism LMWH	0 (0)	1 (1)	0 (0)	1 (<1)
Urinary retention	0 (0)	1 (1)	0 (0)	1 (<1)
Stent integrity issues				
Tapering	1 (1)	11 (6)	5 (6)	17 (5)
Kinking	0 (0)	3 (2)	1 (1)	4 (1)
Fracture	0 (0)	1 (1)	0 (0)	1 (<1)
Angulation	0 (0)	6 (3)	3 (4)	9 (2)
Implosion	0 (0)	4 (2)	1 (1)	5 (1)
Open-surgery related				
Wound infection	N.A.	5* (3)	23 (27)	28 (8)
Seroma	N.A.	1* (1)	5 (6)	6 (2)
lymphorrhea	N.A.	1* (1)	28 (33)	29 (8)
Wound dehiscence	N.A.	0 (0)	10 (12)	10 (3)

Note. Data are n (% of subgroup) unless otherwise indicated. IVCS = iliac vein compression syndrome; P-PTS = post-thrombotic syndrome with percutaneous treatment; H-PTS = post-thrombotic syndrome with hybrid treatment; DVT = deep venous thrombosis; LMWH = low molecular weight heparin; NA = not applicable. ^a Related to secondary open surgical procedures.

However, minor and major bleeding, necessitating supplementary treatment or reintervention, was seen after treatment of 32 (9%) and 13 (4%) patients, respectively, and occurred mainly in the H-PTS group. Of special concern in the hybrid subpopulation was the high incidence of wound related complications, such as wound infections in 23 (27%), lymphorrhoea in 28 (33%), and wound dehiscence in 10 (12%) patients.

Clinical scores

Significant improvement in VCSS was seen in all groups during the first 24 months of follow-up (Figure 23). A significant improvement of Villalta scale was seen for the post-thrombotic patients. A clinically positive treatment effect was seen in 63%, 72%, and 73% of patients in the IVCS, P-PTS, and H-PTS groups, respectively. No response to therapy was seen in 24%, 23%, and 22% of patients, respectively. Worsening of symptomatology was observed in 14%, 5%, and 6% of IVCS, P-PTS, and H-PTS patients. A separate analysis for this non-response group of patients will be performed in future research. Venous claudication was calculated in those patients where a baseline score and at least one follow-up score was available. This reduced in 26/29 (90%) patients with IVCS after a median follow-up of 17 months (range 12-26 months). In 64/78 (82%) P-PTS patients venous claudication was absent after a median of 13 months (range 11-24 months) and in 50/60 (83%) H-PTS patients after 16 months (range 11-25 months). During follow-up, ulceration healed in 20/23 (87%) of the patients presenting with an active ulcer at baseline. However, ulcer recurrence was seen in four (20%) patients.

Figure 23. Venous Clinical Severity Score (VCSS) and Villalta score of the three subpopulations given as clinical scores over 24 months. Note. IVCS = iliac vein compression syndrome; P-PTS = percutaneous post-thrombotic syndrome; H-PTS = post-thrombotic syndrome with hybrid treatment.

DISCUSSION

In this study, the routine clinical use of stenting in 369 patients with PTS and IVCS is described.

Patency rates in patients with IVCS were 90%, 100%, and 100% at 60 months and were comparable with previous studies.^{2,3,4} The main patency related issues were allied to stent geometry and stent placement problems. Regarding this, future outcomes are expected to improve even more with the introduction of dedicated venous stents, as excellent results of a dedicated venous stent during 12 months follow-up already support this.¹⁴

In contrast to the IVCS group, the post-thrombotic subgroups did show stent occlusions. However, secondary patency rates in the P-PTS group were shown to be 89% and comparable with results described in previous reviews.^{2,3,4} The primary patency of 64% in P-PTS patients was most likely lower as a result of inadequate inflow. This is exemplified by the fact that venography during reinterventions frequently showed residual post-thrombotic stenosis distal to the stents. Moreover, patency rates in H-PTS group of 37%, 62%, and 72% at 36 months, proved that impaired flow due to prior thrombosis of the vein tracts below the CFV reduces patency outcomes.

Currently, there is no definitive test available to evaluate the adequacy of inflow prior to stenting or directly after deployment of stents. For this reason, clinical judgment must be relied upon. In general, it is believed that post-thrombotic changes of the CFV below the SFJ with affected orifices of FV and DFV provide inadequate inflow and need a hybrid procedure. Future research should focus on a scoring system to quantify the flow. Afterwards, the evaluation of a cutoff flow value to predict stent inflow and related patency might be performed. Next, decision making based on such a haemodynamic evaluation of DUS, MRV, venography, and IVUS images should be evaluated with respect to the stent patency and clinical outcome. Moreover, if treatment type can be predicted more precisely it is possible to overcome complication related issues, as seen in the H-PTS group.

Since patients in the H-PTS group were more prone to several surgery related complications, like wound infections (27%) and wound dehiscence (12%), the primary patency rate was negatively influenced. Because of the recently disobliterated CFV, this area is more prone to compression by haematomas or lymphocoeles (33%). Moreover, deployed stents are inherently thrombogenic specifically in combination with the stent material and the exposed collagen of the disobliterated area. Furthermore, the AVF may potentially induce intimal hyperplasia causing stenosis of the distal stents or stenosis of the disobliterated area

In all, but especially in patients treated for PTS, the quality of anticoagulation might

be an issue, as it is known that INR values can be inconsistent and influence stent patency. Therefore, a post-operative INR target range of 3e 4 (in accordance with Dutch guidelines) was chosen. Since INR levels are regulated by different specialised entities, an analysis of all INR levels was not possible. Of further note is the fact that interventions, including the surgical disobliteration, were performed on patients already anticoagulated. This has the disadvantage of increasing the rate of postoperative bleeding, though it is believed it is necessary to reduce the risk of early thrombotic stent occlusion. To prevent such an acute stent occlusion, all patients are treated with a preoperative INR level of 2.0e2.5. Oral anticoagulants were stopped 24 hours before the intervention to prevent massive haematomas.

Patients with severe post-thrombotic obstructions, needing a hybrid intervention, have a high risk of complications and reinterventions. However, the hybrid treatment may improve quality of life and pain, and significantly reduce venous claudication when successful. It may be offered to a select group of patients with marked impairment of quality of life and debilitating complaints interfering with daily activities. The hybrid procedure should be discussed with the patient in detail, explaining all possible complications, to make an adequate balanced risk/benefit analysis.

Although favourable results have been presented, there are some limitations to this research, which might cause some bias. As there are no large clinical trials to compare the H-PTS outcomes with, clinical outcomes were partly comparable with previous research, but no response to therapy was seen in 24% of IVCS and 23% of P-PTS patients, respectively.^{2,3,4} Besides this, worsening of complaints was shown in 14% and 5% of patients, respectively. As venous reflux was present at baseline in many patients and was not routinely assessed during follow-up, this non-response might be explained by residual reflux.

In addition, the incompleteness of clinical score data may be a bias in analyzing the treatment effect. Furthermore, especially in the cases of non-response to stenting in IVCS, an initial indication issue might be present. As symptomatic venous disease and anatomical compression of the iliac veins are both common in the Western population, in some patients the compression might not have been the reason for the symptoms.¹¹ Stenting in these patients can be seen as a type of overtreatment. As currently no validated haemodynamic tests exist to assess the relative influence of the iliac vein compression on the lower extremity, it is impossible to differentiate between symptomatic chronic venous compression and anatomical variance in some patients. Future prospective trials should take the above mentioned issues into account to improve optimal care in patients with deep venous obstruction.

CONCLUSION

Percutaneous stent placement to treat non-thrombotic iliac vein lesions, and post-thrombotic iliofemoral obstructions is safe, effective, and showed patency rates comparable with previous research. Patients with advanced disease needing a hybrid procedure showed lower patency rates and more complications. However, when successful, the clinical outcome is favourable at mid-term follow-up and the procedure may be offered to selected patients.

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CHAPTER 9

VENOUS IN-STENT THROMBOSIS TREATED BY ULTRASOUND ACCELERATED CATHETER DIRECTED THROMBOLYSIS

R.H.W. Strijkers¹

M.A.F. de Wolf ¹

C.W.K.P. Arnoldussen^{2,3}

M.J.M. Timbergen³

R. de Graaf²

A.J. Ten Cate-Hoek⁴

C.H.A. Wittens^{1,5}

1 Department of Vascular Surgery and Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, 6202 AZ, Maastricht, The Netherlands

2 Department of Radiology, Maastricht University Medical Centre, 6202 AZ, Maastricht, The Netherlands

3 Department of Radiology, Viecuri Hospital, 5912 BL, Venlo, The Netherlands

4 Laboratory for Clinical Thrombosis and Haemostasis and Laboratory of Haematology, Department of Internal Medicine and Cardiovascular Research Institute Maastricht, 6202 AZ, Maastricht, The Netherlands

5 Department of Vascular Surgery, University Hospital RWTH Aachen, 52074, Aachen, Germany

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ABSTRACT

Introduction

Stent placement in the venous system is an increasingly used treatment modality in chronic venous obstruction and as additional treatment after thrombolytic therapy in iliofemoral DVT. We report on our experience in treating in-stent thrombosis with Ultrasound Accelerated Catheter Directed Thrombolysis (UACDT).

Methods

Retrospective analysis of patients treated for venous stent occlusion, after Percutaneous Transluminal Angioplasty (PTA) and stent placement for either chronic venous occlusive disease or persistent vein compression in patients with acute DVT. Duration of occlusion and suspected clot age were assessed using patient complaints and typical findings on duplex ultrasonography (DUS). DUS and venography were used to assess patency and to determine the cause of reocclusion. Acute treatment of occlusion consisted of UACDT. Additional procedures included: PTA, stent placement, and creation of an arteriovenous-fistula.

Results

We identified 18 patients, who were treated for occluded stent tracts with UACDT between January 2009 and July 2014. Median age was 43 years, and 67% were male. Indications for initial stenting were; treatment of chronic venous obstructive disease in 12 patients and treatment of underlying obstruction after initial thrombolysis in acute DVT in 6 patients. Technical success was achieved in 61% (11/18). Primary patency at last follow-up was 73% (8/11), during median follow-up of 14 months (0-41). Additional treatments after successful lysis were; restenting in 7 patients, and creation of an arteriovenous-fistula in 6 patients

Conclusion

Treatment with ultrasound-accelerated catheter directed thrombolysis of occluded stent tracts is feasible and effective.. Recanalization of the stent tract can be achieved in most cases. Additional interventions were frequently used after successful UACDT treatment. Most stent occlusions were caused by stent related problems.

INTRODUCTION

During the last two decades endovenous recanalization, by percutaneous transluminal angioplasty (PTA) and stenting, in chronic deep venous occlusive disease has quickly gained in popularity. Many authors have shown excellent clinical success rates. 1-3 Because of this, and as stenting seems to be the only treatment aimed at resolving the underlying pathology in post-thrombotic syndrome (PTS) and iliac vein compression syndromes, it has been implemented in many expert-venous centers worldwide as a first-line treatment. Complication rates have been shown to be mild, with generally no clinically relevant pulmonary embolisms and no procedure related mortality. 3-5 The most important complication is acute reocclusion of the stented venous segments, with or without thrombus propagation into proximal or distal vein tracts. This occurs in 20-30% of cases, even when adequate anticoagulation regimens are used.⁴ In cases of stent reocclusion return of signs and symptoms of venous disease can be expected, and in some cases even worsening of complaints compared to the prerecanalization state. An important step in preventing reocclusion is to guarantee adequate in- and outflow for the stents. Inflow problems can arise when veins caudal to the stented segments are also involved in the post-thrombotic process, most notably the femoral and deep femoral vein, as flow volume in those cases might not be sufficient to maintain patency. Outflow problems arise when venous tracts cephalad to the stents are (partly) occluded due to endoluminal pathology or external compression. Furthermore in-stent problems, for example residual compression by overlying arteries or stenosis, kinking or fractures are also thought to lead to higher loss of patency. Prevention by extending stents cephalad or caudal into a healthy vein tract and using stents that withstand the pressure from overlying structures such as arteries and do not kink are therefore very important.⁶ Adequate antithrombotic therapy is also important in preventing rethrombosis.

In cases where reocclusion does occur removal of as much of the thrombus load as quickly as possible is generally thought necessary.⁷ One possible option is to remove the thrombus, by means of pharmacomechanical thrombolysis. Ultrasound accelerated catheter directed thrombolysis (UACDT) is used for acute occlusions in the arterial system, DVT and pulmonary embolism. 8-11 Literature shows good safety and feasibility for UACDT for these indications. Possible advantages of UACDT over the use of a normal thrombolysis catheter are: shortened treatment duration and less thrombolytics used reducing the risk of (major) bleeding.¹² With adequate patient selection, the chance of gaining technical success is around 90% in reported literature associated with minimal bleeding risk.¹³

We report on our experience of treating in-stent thrombosis with UACDT in patients referred to our tertiary center. Furthermore we describe the pitfalls that we have encountered in these cases and provide recommendations how to follow-up on patients after venous stenting.

METHODS

Population

From October 2009 till July 2014 all patients treated for venous stent occlusion by UACDT were eligible for retrospective analysis. All patients were evaluated for bleeding risk. Indication for primary stent placement was either chronic venous occlusive disease or persistent vein compression in patients with acute iliofemoral DVT during thrombolytic therapy. Time between stent placement and occlusion was assessed and divided into two groups (within 6 months after stent placement, and longer than 6 months after stent placement). Occlusion side was noted and if available thrombophilia status was reported. No additional testing for thrombophilia factors was performed. Duration of the occlusion and suspected clot age were assessed using patient complaints and findings on duplex ultrasonography (DUS).¹⁴ Patient complaints were assessed and used as the criterion to categorize patients into two groups; 21 days or shorter interval of complaints and complaints for over 21 days. The last patent duplex scan was taken as a reference value for assessment of clot age. Stent occlusion was diagnosed using DUS with normal B-mode settings, power-flow, e-flow, conventional color and pulse wave Doppler to assess flow in the stent tract. We used at least one of the available modalities or combinations. The venous tract was assessed in both transverse and longitudinal planes. In order to visualize flow in the stented ilio caval tract a number of flow augmenting maneuvers were performed such as inspiration and expiration, dorsiflexion of the foot, and gluteal muscle contraction. Before recanalization and catheter placement, venography was routinely performed, to confirm the diagnosis of stent occlusion. Dutch law allows for retrospective analysis of patient data without specific approval of an ethical committee.

Intervention

The interventional radiologist placed the UACDT catheter under venographic control. The EKOS® Endowave™ Peripheral Lysis System (BTG International Ltd, L) consists of a multilumen infusion catheter with removable, coaxial Ultrasound (US) cores and a control unit that simultaneously delivers high-frequency (2.2 MHz), low-energy (0.45 W) US energy and thrombolytic drug into the thrombus. All patients received UACDT with the EKOS Endowave system. Urokinase (Medacina[®] Lamepro the Netherlands) was in all cases used as the thrombolytic agent. Urokinase was administered with 100 000 units/hour after a single bolus of 250 000 units at the start of treatment. In cases of bilateral occlusion, two catheters were inserted and the drug dosage was evenly divided over the two catheters, each with their own EKOS machine. During thrombolysis fibrinogen levels, Hemoglobin levels (Hb), activated partial thromboplastin time (APTT), prothrombin time standardized to international normalized ratio (INR), thrombocytes and D-dimer levels were routinely monitored. During active thrombolysis, anticoagulant treatment was substituted by intravenous unfractionated heparin guided by APTT (between 40-60 seconds or 1.2-1.7 times the reference value of 34 seconds). At the same

time patients were fitted with intermittent pneumatic compression sleeves. Inferior vena cava filters are not used routinely in our hospital. None of our patients received a caval filter. After thrombolysis, patients either resumed or started oral anticoagulation for at least 6 months or, if indicated lifelong (recurrent DVT). Adequate anticoagulation was achieved with Coumadin with an International normalized ratio (INR) between 2.5 and 3.5 according to the standards of the Dutch federation of thrombosis services (FNT) or Rivaroxaban 20mg once daily. The choice of anticoagulant agent was based on patient preference. Compressive stockings were routinely offered to patients and worn based on preference of the patient. Mobilization was encouraged as much as possible.

Assessment of recanalization

Phlebographic control was performed on a daily basis to monitor thrombolysis progression and to evaluate obstructions in the venous outflow tract. Duration of thrombolysis was determined by assessment of phlebographic imaging and the point where > 90% lysis of the clot was achieved.¹⁵ Thrombolysis was continued in a number of cases, because of bridging towards additional treatment. We tried to determine the cause of the stent thrombosis by means of phlebography from multiple angles. In some cases cone-beam CT was used to create a 3D reconstruction of the stent tract. If the reason for thrombosis of the tract was identified, adequate measures were taken to resolve the problem and prevent future rethrombosis. Objective identification of the underlying cause of stent thrombosis was only possible in patients with successful thrombolysis.

Additional procedures

After successful UACDT procedures, patients received additional interventions if indicated. Additional procedures were performed as soon as possible after successful thrombolysis. Additional procedures such as, percutaneous transluminal angioplasty (PTA) with or without restenting were performed by the interventional radiologist. Surgical procedures to increase inflow such as construction of an AV-fistula between the common femoral vein and artery or endophlebectomy were performed by the vascular surgeon. We used self-expandable stents for stenting for underlying obstructions (sinus-XL[®] and sinus-Venous[®] from Optimed and Zilver vena[™] from Cook[®]). Various diameters and lengths stents were used ranging from 12 to 26 mm in diameter and 60-150 mm in length. Stent sizes were determined by multiplanar venography.

Complications

Complications following thrombolysis and follow-up were categorized into groups. These included bleeding complications, pulmonary embolism (PE), recurrent thrombosis, infections and others. Bleeding was classified as major, if it was overt with a fall in hemoglobin of ≥ 2 g/dl, or when hemorrhage led to transfusion of 2 units of packed red blood cells (RBCs) or whole blood. Bleeding situated in a critical organ (intracranial, retroperitoneal or pericardial) or, if it contributed to death, was also

defined as a major bleeding. Bleeding was classified as minor, if it was situated near the catheter-insertion site.

Follow-up

Standardized follow-up was performed. Patients returned at 2 weeks, 6 weeks, 3 months, 6 months, 1 year, and yearly thereafter. If the patient experienced complaints, follow-up was performed at the earliest convenience, usually the same or the next day. During follow-up patency of the stent tract was assessed using DUS. A dedicated sonographer performed DUS. Recurrence, retreatment, PE, and other complications were recorded. We standardized routine follow-up after stenting in this manner: the day after stenting, patients were checked with DUS to ensure patency of the tract prior to discharge. At 2 weeks, 6 weeks, 3 months and 6 months after stenting the patients were seen with clinical follow-up and routine DUS examination. The complete stented tract was visualized in every patient. Apparent thrombosis and/or lack of flow in the stented tract were used to determine patency.

RESULTS

Patients

A total of 19 legs in 18 patients were treated with UACDT for venous stent thrombosis. The majority of patients were male. The average age of the group was 43 years at time of thrombolysis. In 33% of cases the initial indication for stent placement was to treat an underlying stenosis after acute iliofemoral DVT treatment with UACDT. The remaining 67% received PTA and stenting as a treatment for chronic deep venous obstruction and subsequent complaints. Most stents were placed in the left iliac tract (67%). We noticed that most stent occlusions occurred within 6 months after initial placement of the stents (83% of patients). In 72% ($n=13$) of patients we were able to assess the duration of complaints. In the other cases it was not possible to make an indication of duration of complaints, either because of vague complaints or absence of complaints. Eleven patients were assessed as having acute thrombosis (less than 21 days according to the reporting standards in venous disease). Patient characteristics are summarized in Table 19.

Before the UACDT to treat the in-stent rethrombosis, patients had received a median of 3 (1-13) stents in 1-3 stenting sessions. This was done on the left side in 13, on the right side in 1 and bilaterally in 3 cases; one patient only had stents placed in the inferior caval vein. In all patients Nitinol self-expandable stents were used (sinus XL, sinus repovisual, sinus Venous), in two cases these were combined with Wallstent placement and in one case with balloon-expandable stents (Andramed).

Table 19 shows the baseline characteristics of the patients.

Patiënt characteristics (N=18)	
<u>Gender (male)</u>	67% (n=12)
<u>Age (in years) mean±SD</u>	43±15y
<u>Range</u>	15y - 75y
<u>DVT history</u>	
First DVT	56% (n=10)
Recurrent DVT	44% (n=8)
<u>Primary stent indication</u>	
Acute iliofemoral DVT	33% (n=6)
Chronic venous obstruction	67% (n=12)
<u>Original location stents</u>	
Left iliac tract	73% (n=13)
Right iliac tract	5% (n=1)
Inferior vena cava	5% (n=1)
Inferior vena cava + left and right iliac tract	17% (n=3)
<u>Time between stent placement and stent occlusion</u>	
<6months	83% (n=15)
≥6months	17% (n=3)
<u>Occlusion side</u>	
Left iliac tract	67% (n=12)
Right iliac tract	11% (n=2)
Inferior vena cava	22% (n=4)
<u>Thrombophilia* (7 patients tested)</u>	
Positive	28% (n=5)
Negative	11% (n=2)
Not tested	61% (n=11)
<u>Estimated clot age (days)</u>	
≤21 days	61% (n=11)
>21 days	17% (n=3)
Unclear	22% (n=4)
<u>Days until last patent duplex</u>	
≤21 days	44% (n=8)
>21 days	56% (n=10)

* Encountered thrombophilia: Factor V Leiden, Anti-Thrombin deficiency, protein C deficiency, and antiphospholipid syndrome.

Treatment results and additional procedures

All patients underwent UACDT with the EKOS catheter. Catheter placement was successful in all cases. In 11 of 18 patients patency was successfully regained. This resulted in a 61% technical success rate for this procedure. All patients with failed thrombolysis had an unknown or estimated clot age of over 21 days and last patent duplex more than 21 days ago. Median lysis time of successfully lysed cases was 19 hours

(range: 11-101). In five cases we performed additional stenting and created an AV-fistula to treat an underlying cause such as stenotic lesions not treated previously. Figures 24 and 25 show pre- and post-thrombolysis results. Furthermore we encountered stent related occlusions and insufficient inflow in the stent tract. In two cases we performed additional stenting and in one patient we secured inflow of the stent tract with the creation of an AV-fistula. In total 8/11 (73%) patients needed ancillary interventions after successful thrombolysis. In all cases of UACDT we identified the underlying causes of rethrombosis. These were; suboptimal positioning, failure due to stent characteristics (kinking of stents and stent fracture), insufficient inflow or inadequate anticoagulation. Figure 26 shows an example of stent fracture in the venous system. Most occlusions we encountered were related to stent failure and suboptimal positioning. Table 20 shows the treatment results. Table 21 shows the time between last patent duplex and occlusion, suspected clot age, and suspected reason for reocclusion.

Figure 24. (A) In situ sinus venous stent in the left common iliac vein. (B) Digital subtraction venography with the catheter in the common femoral vein shows contrast filling of the external and internal iliac veins. There is no filling of the (occluded) stent in the common iliac vein. (C) Recanalization of the stent with outflow of contrast to the inferior vena cava. (D) Placement of the EKOS Endowave Peripheral Lysis System (BTG International Ltd, London, UK) thrombolysis catheter through the occluded stent.

Figure 25. (A) Control venography after extended thrombolysis and balloon angioplasty shows an open lumen with outflow to the inferior vena cava (B) Extension of the stented deep vein tract to the inferior vena cava and external iliac vein to cover the entire deep vein obstruction (C) Control venography after stenting and balloon angioplasty shows improved (out) flow through the iliac veins with persistent filling of presacral collaterals. (D) Final control venography after additional balloon angioplasty shows adequate flow from the groin to the inferior vena cava without filling of collaterals.

Figure 26. Fractures of the rigid Sinus XL stents in the distal external iliac vein / proximal common femoral vein are seen (arrow).

Table 20 Treatment results

UACDT procedures (N=18)	
<u>Successful thrombolysis?</u>	
Successful	61% (n=11)
Not successful	39% (n=7)
<u>Duration of successful thrombolysis (n=11)</u>	
Median	19 hours
Range	11-101 hours
<u>Restenting after successful UACDT (n=11)</u>	
	64% (n=7)
<u>Other additional interventions after successful UACDT (n=11)</u>	
Arteriovenous fistula	55% (n=6)

Table 21 Reocclusion cases

Patient	Days since last patent duplex	Suspected slot age ≤21 days >21 days unknown	Lysis successful Yes/No	Reason for occlusion*
1	120	≤21 days	Yes	1
2	15	≤21 days	Yes	1,2
3	5	≤21 days	Yes	1
4	0	≤21 days	Yes	3
5	9	≤21 days	Yes	1
6	9	≤21 days	Yes	1,2
7	5	≤21 days	Yes	1,2
8	42	≤21 days	Yes	1
9	10	≤21 days	Yes	1,2
10	41	≤21 days	Yes	2,4
11	21	≤21 days	Yes	3
12	56	≤21 days	No	1
13	83	Unknown	No	1
14	120	Unknown	No	1
15	40	Unknown	No	1,2
16	35	>21 days	No	1
17	30	Unknown	No	1
18	93	>21 days	No	1

*1 stent related failure e.g. stent fracture, kinking), 2 suboptimal stent position, 3 inadequate inflow, 4 failed anticoagulation

Complications

In total 6 patients experienced adverse events. During UACDT 2 patients had a hemoglobin decrease without a bleeding focus, which necessitated erythrocyte transfusion. One patient had minor bleeding at the catheter insertion site that

was solved with manual compression. One patient experienced heparin-induced thrombocytopenia. Heparin was switched for argatroban intravenous for the further duration of UACDT. One patient complained of blepharo edema and urticaria, which was recognized as an allergic reaction to iodine contrast fluid used for venographic control unrelated to thrombolytic therapy. One patient had fever with positive blood cultures during thrombolysis. In this patient thrombolysis was stopped and treatment with antibiotics was started. None of the patients experienced multiple complications. We did not encounter any clinically relevant pulmonary embolism or treatment related mortality Table 22 is an overview of all complications encountered during UACDT.

Table 22 Complications

Patients (n=18)	N (%)
Minor bleeding ^a	1 (5)
Major bleeding ^b	2 (11)
Pulmonary embolism	0 (0)
Death	0 (0)
Other ^c	3 (17)

^a Epistaxis, catheter insertion site.

^b Drop in hemoglobin needing red blood cell transfusion.

^c Allergic reaction, infection, heparin induced thrombocytopenia.

Follow-up

Regarding all successfully lysed patients (n=11), 8 remained patent, which translates into a primary patency of 73%. Seven patients experienced complete relief of complaints and two patients had partial relief of complaints. One patients did not benefit from UACDT with regard to relief of complaints. In one case there was an immediate reocclusion the day after successful lysis, due to stent related problems. Table 23 shows the follow-up data for the successfully lysed patients.

Table 23 Follow up data

Follow-up n=11	
<u>Follow-up length</u>	12 months
<u>Median in months (range)</u>	(0-41)
<u>Patency at follow-up</u>	
Patent	73% (n=8)
Occluded	27% (n=3)
<u>Relief of complaints</u>	
Complete relief	64% (n=7)
Partial relief	18% (n=2)
No relief	9% (n=1)
unknown	9% (n=1)

DISCUSSION

With the growing number of effective thrombolytic treatments in acute iliofemoral DVT, we expect that an increasing number of patients will be additionally stented for residual stenotic lesions. Some reports show over 50% of patients are to be stented after thrombolysis.¹⁶ At the same time there are also more interventions performed in patients with post-thrombotic syndrome due to extensive chronic occlusions in the iliocaaval tract. As both of these procedures gain in popularity, it can be expected that more venous stenting related complications will be encountered.

We identified reocclusion to be the most frequent and clinically important complication after venous stenting and by our knowledge we are the first to specifically focus on how to treat this important complication. Earlier studies also addressed stent occlusions to be an important complication after venous stenting.^{4,5,17}

We report a technically successful recanalization of occluded stents in the venous system of 61% and a primary patency of 73% after a median follow-up of 12 months. In all cases it was possible to get a wire across the occluded segments. In all cases we intended to treat the stent occlusions with a suggested thrombus age of less than 21 days based on complaints or homogeneity on DUS. Thrombolysis within 21 days seems to result in more success than interventions at a later moment in our series. Although there is one report on successful interventions in the chronic DVT phase, we could not reproduce these findings.¹⁸ We believe it is important to accurately assess the time of onset of the thrombosis. We found that patient reported duration of complaints was not useful to determine thrombus age and therefore the success rate of the thrombolysis was not predictable. Other techniques like MR-venography, DUS elastography, or intra vascular ultrasound might prove more useful in determining the thrombus age, better predict outcome and be used for patient selection.¹⁹

Regarding the specific usefulness of UACDT in regaining patency, we report a median lysis time to lyse 90% of the thrombus of 19 hours, which is fairly quick. However in some cases we continued the lysis treatment until the necessary additional procedures could be performed. We encountered two rare complications; HIT and contrast allergy. Two major bleedings requiring transfusion were encountered. Other complications involved catheter insertion site bleeding, which were very minor, and therefore we may conclude that UACDT is a safe procedure. Many stent related flow-complications result in reocclusion of the venous tract. Occlusion of the stent tract nullifies the progress gained by the initial treatment. When encountered in an early stage, the thrombosed stent tract can be cleared by thrombolysis.⁴ Patency can be regained and most importantly the underlying cause of occlusion can be identified or should be identified during the procedure. UACDT is one of the available options for regaining patency. Other clot removal therapies can also be used for this purpose.²⁰

In all cases of successful thrombolysis the underlying cause of the occlusion was identified. Also in the not successful thrombolysis group we identified stent related causes for occlusion. In total in 15 of all 18 cases we identified stent related failures

like kinking, fracture and continuous compression of the stents. These stent related problems are potentially due to the stent characteristics. The stents used in this study are primarily designed for arterial use. With new, dedicated venous stents we expect to prevent future stent related occlusions. Ideally, dedicated venous stent with high flexibility, high radial force and large diameters are used in the venous system.²¹ A number of dedicated venous stents have become commercially available.

Most of the occlusions occurred within 6 months after the initial stenting. A rigid follow-up of patients is therefore paramount. The frequent follow up allowed for timely interventions with UACDT in case reocclusion occurred. At the 6-month visit continuation of anticoagulation was evaluated based on stent configuration, patient risk factors and patient preference. Thrombocyte aggregation inhibitors were not routinely prescribed following cessation of Coumadin although they might be of influence. If at any point between follow-up visits patients experienced complaints, they were seen at the earliest convenience. After 6 months follow-up visits were planned at one year after stenting and afterwards yearly, depending on patient preference.

The most difficult problem we encountered is the patient with bad inflow due to extensive chronic venous occlusive disease with scarring in both major inflow vessels (i.e. femoral and deep femoral vein.). In these patients we noticed the impaired inflow due to extensive scarring of both the femoral and deep femoral vein. At the moment there are no reported successful treatments available for these veins. Endophlebectomy with or without AV-fistula has been described in literature as a treatment option in these cases.²²⁻²⁴ Stenting might be a possibility for these veins, however the current available material is not suitable for placement in the femoral or deep femoral tract. To reassure adequate inflow in the patient we currently rely on the creation of a temporary AV-fistula, with or without an endophlebectomy of the common femoral vein to secure adequate inflow into the stented tract.²⁵ Further research is needed to improve care in these cases.

One of the drawbacks of our study is the retrospective nature. The expected number of cases per year, %er is expected to be very low, which would makes it challenging to complete a prospective study. Optimal registration of patient data and pooling of results from retrospective studies could improve patient care considerably. We therefore would like to encourage other centers to report on their experience regarding stent thrombosis and its treatment.

CONCLUSION

Treatment with UACDT of occluded stent tracts is feasible and effective. Recanalization of the stent tract can be achieved in some cases with recent thrombosis less than 21 days. Additional interventions were frequently necessary after successful UACDT treatment. Most stent occlusions were caused by stent related problems.

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CHAPTER 10
SUMMARY AND GENERAL DISCUSSION

Chronic venous disease is pathophysiologically compromised of two distinct mechanisms: venous insufficiency (incompetent venous valves leading to retrograde flow; reflux) and venous obstruction (the lumen of a vein is, partly or totally, blocked).^(1, 2) Venous obstruction can be present in all vein segments, but is clinically most relevant in the major outflow tracts.⁽³⁻⁶⁾ In the lower extremity the major outflow tracts are the deep veins, and to a lesser extent the great and small saphenous veins. The most important sources of deep venous obstruction are external compression of the vein (iliac vein compression syndrome; IVCS), and deep venous thrombosis (DVT); both in the acute phase and especially at the long term.⁽⁷⁻¹²⁾ In the latter case it is termed the post-thrombotic syndrome (PTS), as chronic obstruction caused by the DVT-associated inflammatory response decreases outflow. There are currently numerous ways to remove a thrombus in the acute setting, all of these techniques hope to prevent PTS on the long term; these novel techniques however are beyond the scope of this thesis.^(13, 14) Treatment options aimed at chronic venous obstruction can be divided in three types. Firstly, conservative treatment, consisting mainly of compression therapy, and to a lesser extent pharmaceuticals.⁽¹⁰⁻¹²⁾ Conservative treatment is currently still the cornerstone of PTS-treatment in most countries and practices. Secondly, bypass surgery, either crossover bypasses (de Palma bypass, from the ipsilateral common femoral vein to the contralateral common femoral vein) or in-line veno-venous bypasses.⁽¹⁵⁾ This type of open surgery has historically been reserved for the most severe cases of PTS (patients that were totally unresponsive to conservative treatment), because of its rather invasive character. And thirdly, percutaneous transluminal angioplasty (or venoplasty) and stenting, which has become available during the last three decades through technical advances in the field of interventional radiology.⁽¹⁶⁻²⁵⁾ The advent of these endovenous treatment modalities has made venous bypass surgery obsolete, in all but those cases in which both conservative treatment and PTA & stenting have failed. Conservative treatment itself however is still a valuable addition to endovascular therapy, in PTS and IVCS patients in whom PTA and stenting are not indicated, and in sole deep venous valvular insufficiency.

WHO SUFFERS FROM PTS?

DVT is a relatively prevalent disease and, because many DVT patients will develop chronic complications, so is PTS.^(8, 9, 26) Extensive research has been conducted aimed at epidemiology and prevention of PTS, however its exact incidence differs greatly between studies. As is shown in chapter 2, most recent studies show incidence rates generally between being 20% and 80% for PTS as a whole, and between 5% and 25% for severe PTS. Differences are best explained by the difference in target population and varying definitions of PTS between studies. Many risk factors for PTS development have been evaluated, the most significant in daily practice being: age, obesity, gender, ipsilateral recurrence of DVT, the location of the initial thrombus (proximal vs distal),

and the presence and degree of residual occlusion and reflux post-DVT. Some of these risk factors of course can't be influenced in patients, and others only underscore the importance of conservative therapy in reducing the risk of PTS-development. Moreover, measurements of inflammatory markers, adhesion molecules and other measurable values in DVT patients show promise in working towards a more tailored risk stratification and thereby possibly an individualized secondary prevention protocol in DVT patients.

Looking at the demographics of the follow-up studies presented in this thesis (those in chapters 3-5 and 7-9), a number of observations about the population generally presenting for treatment of their PTS and IVCS can be made. Most are female and these patients are generally young, in their early forties, when treated. The time between a first DVT and the moment of treatment is approximately 10 years in our studies. Symptomatic PTS generally reveals itself 6-24 months after a DVT. Therefore, the PTS patients who present themselves at our clinic are generally young working mothers, who can be severely inhibited in their busy daily routine. The potential to significantly improve the lives of these patients and their families is therefore grand. The fact that risk of DVT and PTS increases with age, of course doesn't correspond with this fact of low average age of the patients treated in our studies. The contrast can probably be best explained by a physician-bias in offering stenting and hybrid procedures to patients who are still more (physically) active in life.

WHO TO STENT?

Whereas the indications for treating patients suffering an acute DVT are clear and well established world-wide, in PTS quite the opposite is true. Literature has suggested that PTS can be prevented by use of compression therapy in the months to years following the thrombosis.(10-12) However consensus is lacking on what treatment needs to be offered to what patients. In our studies we included patients based on two major criteria. The first being anatomical in nature: patients who are to be stented logically need one or more stentable lesions in their venous system. Secondly, patients need to suffer on a level of severity which makes offering them an (minimally invasive, however still invasive) intervention acceptable.

The presence of stentable lesions and the severity of obstruction was evaluated by use of two main imaging modalities in our studies. Duplex ultrasonography (DUS) was used to evaluate the levels of obstruction and the degree of stenosis per segment. Magnetic resonance venography (MRV) was used for the same reason, the advantages of MRV being: non-user dependability and the ability to create an overview of the venous system in a patient which DUS cannot do.(5, 27) DUS itself has the advantage of being more dynamic and it also has the possibility to assess venous reflux/valvular insufficiency (one of the two main pathological pathways of PTS). Moreover, DUS is

used in the follow-up period to assess stent patency (the “openness” of the stent) or the presence and degree of any stenosis. Of course we also used multiplane venography to assess the to-be-treated vessels at the time of the intervention.

One of the most important roles of imaging was to assign patients to one of the three treatment subgroups: IVCS, sole endovascular treatable PTS or hybrid treatable PTS. The combination of a lack of a medical history of DVT, the lack of post-thrombotic vein scarring, and the presence of extra-luminal compression on the iliac veins leads to patients being assigned to the IVCS subgroup. In patients who did show post-thrombotic venous scarring on imaging one important distinction was necessary for adequate treatment planning: the presence or absence of involvement of the inflow vessels of the common femoral vein in the post-thrombotic disease process. In a minority of patients inflow into the to-be-stented vein tract was deemed inadequate based on the DUS and MRV imaging, however it was judged that open-surgical removal of the post-thrombotic intraluminal scar tissue would be possible to mitigate the inflow problems. In those cases patients were allocated to the hybrid treatment subgroup. In addition to the removal of scar tissue, an arterio-venous fistula was created to counteract the increased thrombogenic state post-operatively. When it was expected that future stent inflow would be no issue, sole-endovascular treatment was planned for the patients. Ultimately this led to a distribution of half of the patients being treated purely endovascularly for PTS, a quarter being treated in a hybrid fashion for PTS and the remaining quarter being treated endovascularly for IVCS.

The assessment of the level of severity of signs and symptoms in patients was more subjective; any patient suffering to a degree of which the treating physician found it significant enough to offer stent placement or a hybrid treatment was accepted. Generally these patients scored high in the CEAP classification, venous clinical severity score (VCSS) and Villalta scales (the higher the score the higher the severity), however this was not the case in a significant amount of patients. The reason for this lies in the fact that none of these scoring systems include important issues such as venous claudication or inability to function normally in daily life. We therefore chose to use these scoring systems as a measurement of effect after stenting, but they were not used for inclusion into the studies on.

HOW DO THE STENTS PERFORM TECHNICALLY?

Stents are placed to open up a vessel which was previously partially obstructed or totally occluded, therefore first and foremost stents need to stay patent as long as possible, ideally lifelong. In roughly 65-90% of cases patients were stented and that was it: no second intervention was needed and the stents remained patent for the rest of the follow-up period (this is called primary patency). In a number of cases a second intervention was needed to keep the stented vein segments patent during follow-up,

however no reocclusion occurred in these patients (this is called assisted primary patency. In cases such an assisted primary intervention was necessary, 80-99% remained patent during follow-up. In other patients a second intervention was needed to reopen stents which reoccluded during follow-up (this is called secondary patency). After such interventions, 90-100% remained patent during the follow-up period.

These patency rates varied somewhat between studies, differences were mainly due to two reasons: the differences in length of follow-up and the exact type of intervention. Most stents which reoccluded seemed to do so during the first year after placement. However, even after this period some stents reoccluded. Therefore it is logically that the studies with a longer follow-up period had lower patency rates. More important for patency rates are the technical details of the intervention. In patients suffering from more severe post-thrombotic lesions, more aggressive techniques were generally used, and therefore patency rate during follow-up was lower. This is best shown in the differences between patients stented for PTS and IVCS, with the latter faring better. Another difference is the type of stent used in a patient. When starting in 2009 we used relatively rigid stents, because no other were available with the desired radial force. This rigidity in the venous system led to stents kinking and fracturing in a number of cases, and thereby necessitating re-interventions leading to reduced (primary) patency rates.

Of special note are the cases in which a surgical desobstruction of the common femoral vein (endophlebectomy) was combined with stenting (the so called hybrid treatment) and the cases in which the deep venous system of both legs was treated (unilateral treatment vs bilateral treatment).(28) In the hybrid cases patency rates were much lower compared to sole stenting procedure; primary patency was 35-50%, assisted primary patency was 60-70% and secondary patency was 70-85% in the hybrid subpopulation. The reason for this is twofold. Firstly patients needing a hybrid treatment had the most severe post-thrombotic damage to their vein systems to begin with, leading to a lower overall quality of their venous system. Secondly the open surgery had a relatively strong thrombogenic effect, for this reason the arterio-venous (AV) fistulas were needed, but still the change of rethrombosis was relatively high. Moreover, we suspect that the AV-fistula itself might have played a role in a number of losses of primary patency as it is known that the specific flow conduction created by AV-fistulas can lead to intimal hyperplasia and stenosis. And again, in this population length of follow-up and the stent types used had an influence on the patency rates. In the bilaterally treated patients patency rates were also somewhat reduced compared to only unilaterally stenting. Also in these patients more severe post-thrombotic vein damage was present in the deep veins which led to a lower quality venous system. Of special note in this population is that in many cases not only the ilio-femoral tracts were affected, but also the inferior vena cava, adding to the severity and extensiveness of the disease.

Do patients improve in their symptoms?

As already stated above the scoring systems in use in venous literature, namely the VCSS, Villalta scale and the CEAP scoring system, are less than ideal as they are lacking some important symptoms of PTS.(29-33) Nevertheless we chose to use these because of lack of better tools. Moreover these scores are validated in international literature and are frequently used in other studies. To partly mitigate the absence of specific venous claudication scoring in these three scoring systems we chose to score the absence or presence of venous claudication separately.(34) In contrast to the three validated scoring systems this claudication scoring is not validated. We therefore chose to keep it as simple as possible by not assigning any grade of severity to claudication in patients. Of special note, in light of patients' follow-up is the CEAP score, which is known to be insensitive to changes over time. For this reason we chose to only use the CEAP score as a tool to describe our population at baseline, and neglect it for any follow-up analyses.

Overall we saw clinically and statistically relevant improvements in patients' signs and symptoms in all the follow-up studies (those in chapters 3-5 and 7-9). VCSS scores generally dropped 2-3 points during 1 – 2 years follow up in all three treatment groups; i.e. IVCS, endovascular-treated PTS and hybrid-treated PTS. Villalta scores dropped 5-7 points in the same groups during the same follow-up. Venous claudication subsided in about 70-90% of patients who were noted to suffer from it at baseline measurement. There were no great differences in the absolute number of points, the scores decreased over the three treatment subgroups, however the number of points at baseline was generally a bit lower in IVCS patients compared to endovenous-treated PTS patients, and a bit higher in the hybrid-treated patients. Ulcer healing rates and recurrence rates were also noted in these studies; most ulcers healed (ca. 80%) and most did not recur during follow-up (ca. 20% recurrence).

Worsening of symptomatology, expressed as increase in VCSS and/or Villalta score, was seen in less than 10% of treated patients, and was most prevalent in the IVCS subpopulation. From our studies it is unclear if this is a temporary issue or reflects long-term clinical worsening. Moreover, the relation to loss of patency or other complications is unclear, as it is true that a number of patients with patent stents (especially in the IVCS population) showed increase in clinical scores post-stenting and a number of patients with occluded stent during follow-up showed improved clinical scores.

Also of note is the already stated fact that many patients were treated years after their first DVT; the main time between the DVT and stenting was 10 years, and some patients were treated many decades after their first DVT. This forms an important distinction between stenting in PTS and the prevention of PTS by thrombolysis or thrombectomy, which is characterized by the fact that these preventive techniques suffer from a very narrow treatment window. Moreover this means that practically all PTS patients with sufficient symptoms could at this moment be treated.

WHAT ARE THE DOWNSIDES TO STENTING?

All in all, the complications noted in all studies were deemed acceptable. Indeed PTA and stenting is generally well tolerated by patients, and complications which do occur are generally mild and temporary. In cases in which a hybrid approach is used, complications are more frequent and more severe, however most are still confined to the immediate post-operative period. In both endovenous and hybrid interventions reocclusion is the most important complication, this is in line with literature.⁽¹⁵⁻²⁵⁾ In patients treated because of IVCS however, in contrast to reports by many other authors, no occlusions of the stents have been noted. All loss of primary patency in this subgroup was related to renewed or persistent stenosis after stenting, reasons for this included; compression on stents, stents which were misplaced (placed distally of the compression) and other types of stent-failure. The underlying reasons for reocclusion in the PTS population are thought to relate to problems on one of three levels; inflow into the stents at the level below stenting, at the level of the stents themselves or at the level of outflow above the stents. As we always tried to land stents in healthy vein segments, so above and below the post-thrombotic aberrations, we aimed to reduce inflow and outflow problems. This was generally easily manageable at the outflow end, because mostly post-thrombotic synechiae ended at the caval confluence, so stenting into the cava was generally not needed. However, these synechiae frequently did continue into the femoral and deep femoral veins, which put the inflow into the stents at risk. Of course this was the reason to perform a hybrid procedure in many cases, but with or without the endophlebectomy and AV-fistula, the lesions in the distal femoral, popliteal and deep femoral vein were left untouched. Therefore we suspect inflow problems might have had a significant influence on patency rates. Other important potential influences on patency were on the level of the stents themselves, these included; stent-geometrical problems (such as angulation and articulation between different stents), inadequate anticoagulation (relatively low INR in some patients), extrinsic compression on the stents or endophlebectomy area (for example hematoma or lymphoma which developed after the open-surgical part of the hybrid procedure) or stenosis due to intimal hyperplasia caused by the AV-fistula.

On the long term the restenosis and reocclusions were the only important complications. However, on the short term there were a number of issues related to the invasiveness of the procedures. In the patients treated in a solely endovascular manner the only important complications were related to bleeding, with minor bleeding complications occurring in less than 10 percent, and major bleeding complications occurring in less than 1 percent. The most important contributing factor being the fact that procedures were performed in patients who were anticoagulated at the time of the intervention, which logically increased bleeding risk. In the patients treated by hybrid procedures bleeding complications were more frequent (both major and minor complications occurring in circa 15 percent of patients). In these patients the procedures were also

performed under full anticoagulation, but of course the surgical trauma was much more severe compared to the endovascularly treated patients. Other important complications in the hybrid subpopulation were also related to surgical trauma, these being: wound infection (circa 30 percent), wound dehiscence (circa 10 percent) and lymphorrhea (circa 40 percent). These complications were generally well manageable and had little to no influence on the long term results of the procedure. However, they were a great source of morbidity on the short term and as such an increased length of hospital stay and a prolonged time until patients were fully mobile again post-intervention. Of note is the fact that there were no clinically evident pulmonary embolisms during follow-up, and also mortality of other causes was nil.

WHAT MIGHT THE FUTURE BRING?

During the time this thesis was underway, endovascular treatment of IVCS and PTS has become an accepted treatment option worldwide, exemplified in the inclusion of it in many recent guidelines. As such commercial interest has quickly increased, many new tools are quickly becoming available as we speak. Arguably the most important being new types of stents, optimized for use in the venous system. There will probably be a continuation of this trend, with new stents becoming available and others being optimized. Even though logically these might seem superior to the “old” stents, there is currently little to no evidence to back this up. Direct comparison between stents will be needed, however it is questionable if that type of study will be performed in the near future. Of course the most advancements can be made in the group which performs the worst, in this case the patients suffering from extensive PTS who are treated by hybrid means. As frequently the endophlebectomized area tends to stenose or collapse during (early) follow-up, reinforcement of this vein segment might increase early patency rates. One way would be to leave a fixed-diameter stent-like device or inlay in the area post-surgery, preventing collapse or compression (by haematoma or lymphocele). Ideally however one would forego the open-surgical part altogether and also use purely endovascular means in the patients with these most extensive post-thrombotic aberrations. Stenting through the common femoral vein and into the femoral or deep femoral vein might be possible and if so be superior compared to the hybrid procedure, as this will mitigate many of the open-surgery related issues.

However, the greatest possibilities for advancement in the field of PTS lie within prevention. Currently a multitude of tools and techniques, both chemical and mechanical in nature, are becoming available which are all aimed at removing the thrombus in the acute phase of the disease. Currently the first clinical results are somewhat disappointing, but in time these modalities might make PTS a disease of the past. This will leave IVCS however, still necessitating PTA and stent placement in the venous system.

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ADDENDA

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NEDERLANDSE SAMENVATTING

Chronisch veneuze ziekte kan pathofysiologisch ingedeeld worden in een tweetal mechanismen; veneuze insufficiëntie (incompetente, lekkende veneuze kleppen leiden tot retrograde flow, dit noemt men ook wel reflux) en veneuze obstructie (het lumen van een vene wordt gedeeltelijk of in zijn totaliteit geblokkeerd). Veneuze obstructie kan in principe vóórkomen in alle veneuze segmenten in het lichaam, maar klinisch is dit het meest relevant in de grote venen. In de onderste extremiteiten betreffen dit de diepe venen en in mindere mate de vena saphena magna en parva. De belangrijkste oorzaken van diep veneuze obstructie zijn externe compressie op de vene (iliacaal veneus compressie syndroom, IVCS) en diep veneuze trombose (DVT); zowel in de acute fase als op de lange termijn. In geval van lange termijn problematiek in het kader van DVT spreekt men van het post-trombotisch syndroom (PTS). Dit betreft de chronische obstructie in een vene die wordt veroorzaakt door de (lokale) inflammatoire reactie die samengaat met een DVT. Momenteel zijn er meerdere technieken beschikbaar om een trombus in de acute fase te verwijderen (de meeste hiervan worden overigens in het algemeen nog als relatief experimenteel gezien). Al deze technieken zijn er op gericht PTS op de (middel)lange termijn te voorkomen, deze technologieën liggen echter buiten het bereik van deze thesis. Behandelopties gericht op chronisch veneuze obstructie kunnen worden ingedeeld in drie typen.

1. Conservatieve behandeling: deze bestaat voornamelijk uit het gebruik van compressietherapie en in mindere mate van medicijnen. Conservatieve therapie is momenteel nog steeds de hoeksteen van de behandeling van PTS in de meeste landen en klinieken.
2. Bypass chirurgie: deze behandeling bestaat uit het aanleggen van ofwel een “cross-over” bypass (de Palma operatie, er wordt een bypass gecreëerd van de ipsilaterale vena femoralis communis naar de contralaterale vena femoralis communis) ofwel een “in-line” bypass (het creëren van een bypass door deze ipsilateraal voor en na de obstructie te anastomoser). Deze types chirurgie zijn historisch altijd gereserveerd geweest voor de meest ernstige gevallen van PTS (ergo: ernstige klachten en geen respons op conservatieve behandeling) omwille van het invasieve karakter van deze ingrepen.
3. Percutane transluminale angioplastiek (PTA, ofwel “dotteren”, een endoveneuze techniek) gecombineerd met stenting: deze technieken zijn de laatste drie decennia beschikbaar gekomen uit technische vooruitgangen binnen de interventie radiologie. Hierbij blaast men een speciaal type ballon op in de vene die geobstrueerd/geoccludeerd is met als gevolg dat het bloedvat weer “open” is, vervolgens laat men een stent achter (een soort metalen veertje) om het bloedvat ook op de lange termijn open te houden.

Door de komst van deze endoveneuze behandelingsoptie is de veneuze bypasschirurgie obsoleet geworden in de meeste gevallen. Conservatieve therapie is nog steeds een waardevolle additie aan de endoveneuze therapie; in gevallen van PTS en IVCS waarvoor stenting niet geïndiceerd is en in solitaire diep veneuze insufficiëntie.

Welke patiënten lijden aan PTS?

DVT is een relatief veel voorkomende ziekte en omdat veel patiënten chronische complicaties van DVT zullen ontwikkelen is PTS dat ook. Men heeft uitgebreid wetenschappelijk onderzoek gedaan naar de epidemiologische aspecten van PTS en de preventie hiervan, echter verschilt de exacte incidentie sterk tussen verschillende studies. Zoals men in hoofdstuk 2 kan lezen laten de meeste recente studies een incidentie zien tussen de 20 en 80 procent voor PTS in het algemeen en tussen de 5 en 25 procent voor ernstige PTS. Verschillen in deze percentages kunnen verklaard worden door andere onderzoekspopulaties en verschillende definities van (ernstige) PTS. Veel risicofactoren voor de ontwikkeling van PTS zijn in de loop van de jaren onderzocht, de meest significante voor de dagelijkse klinische praktijk zijn; leeftijd, de aanwezigheid van obesitas, geslacht, een tweede episode van DVT ipsilateraal, de locatie van de initiële trombose (proximaal of distaal) en de aanwezigheid van residuale obstructie en/of reflux. Een aantal van deze risico factoren zijn uiteraard niet aan te pakken bij patiënten. Anderen laten echter zien wat het belang van adequate conservatieve therapie is na een DVT. Daarnaast zijn er meetbare stoffen in het bloed van patiënten, zoals inflammatoire markers en adhesie moleculen, die mogelijk in de toekomst kunnen bijdrage bij het creëren van een gepersonaliseerd risicoprofiel en geïndividualiseerde secundaire preventie.

Wanneer we kijken naar de demografische gegevens van de patiënten in de follow-up studies in deze thesis (hoofdstukken 3-5 en 7-9), kunnen we een aantal observaties doen over de populatie die zich in het algemeen presenteert met PTS en IVCS in onze kliniek. Er is een voorkeur voor het vrouwelijk geslacht en de meeste patiënten zijn relatief jong, begin veertig, op het moment van behandeling. De patiënten bestaan dus voor een belangrijk deel uit werkende jonge moeders, die ernstig beperkt worden in hun dagelijkse routine. De mogelijkheid om de levens van deze patiënten en hun families te verbeteren is daarom erg belangrijk. Het feit dat het risico op het ontwikkelen van een DVT en PTS toeneemt met de leeftijd komt uiteraard niet overeen met deze relatief jonge leeftijd bij presentatie van patiënten in ons centrum. Vermoedelijk is dit deels te verklaren vanuit een verwijzers-bias of behandelaars-bias voor het aanbieden van deze therapie aan patiënten die nog (fysiek) actief zijn in hun leven.

Welke patiënten kan men stenten?

Hoewel de indicaties voor het behandelen van een acute DVT wereldwijd relatief uniform geaccepteerd zijn, is voor het PTS juist het tegenovergestelde waar. De literatuur stelt dat PTS voorkomen kan worden bij een significant aantal mensen door het gebruik van compressietherapie in de maanden tot jaren na de DVT. Echter mist er consensus betreffende welke andere therapieën aangeboden kunnen/moeten aan welke PTS-patiënten. In onze studies was inclusie gebaseerd op twee belangrijke criteria. Allereerst moet er sprake zijn van een anatomische obstructie in het diepe venenstelsel welke stentbaar geacht wordt. Ten tweede moet de patiënt dermate ernstige klachten ondervinden dat een (minimaal invasieve, doch nog steeds invasieve) interventie acceptabel is.

De aanwezigheid van stentbare laesies en de ernst van obstructie hebben wij geëvalueerd

middels twee beeldvormende technieken. Duplex ultrasonografie (DUS) is gebruikt om de niveaus van obstructie en de mate van stenose per segment te evalueren. Magnetische resonantie venografie (MRV) is gebruikt om dezelfde redenen. De voordelen van MRV boven DUS zijn dat de kwaliteit van het onderzoek niet afhangt van de uitvoerder en het feit dat met MRV een overzichtelijk beeld kan worden gemaakt van het gehele veneuze systeem. DUS heeft aan de andere kant weer het voordeel dat het erg dynamisch is en dat hiermee ook veneuze reflux kan worden geëvalueerd. Bovendien hebben wij DUS gebruikt tijdens follow-up om de “patency” (ofwel de openheid) van de stents te beoordelen. Hiernaast hebben wij uiteraard ook gebruik gemaakt van conventionele venografie om de te behandelen vaten te beoordelen ten tijde van de interventie.

Eén van de belangrijkste taken van de beeldvorming was de ondersteuning in het indelen van de patiënten in drie subgroepen; de IVCS-patiënten, de PTS-patiënten die geholpen zouden gaan worden middels puur endovasculaire technieken (PTA en stenting) en de patiënten bij wie een combinatie nodig zou zijn van endovasculaire behandeling en open-chirurgie (de hybride behandeling). De combinatie van een afwezigheid van DVT in de voorgeschiedenis, geen post-trombotische verlittekening in de vaten op beeldvorming en de aanwezigheid van extraluminale compressie op een diepe vene brachten patiënten in de IVCS-subgroep. In patiënten bij wie wel post-trombotische verlittekening aanwezig was in de diepe venen was het van belang te weten in welke mate de inflow vaten van de vena femoralis communis betrokken waren bij de ziekte. Bij een minderheid van de patiënten werd deze inflow onvoldoende geacht voor een puur endovasculaire ingreep, deze patiënten werd een hybride ingreep aangeboden. Hierbij wordt de vena femoralis communis chirurgisch geopend en het post-trombotische littekenweefsel voorzichtig verwijderd met het idee dat hierdoor de inflow in de stents (die meer craniaal geplaatst worden) verbeterd wordt. Dit wordt de hybride ingreep genoemd, daar endovasculaire technieken worden gecombineerd met open-chirurgie. Naast het verwijderen van dit littekenweefsel wordt ook een arterioveneuze fistel (AVF) aangelegd, dit om de erg trombogene status per- en postoperatief te attaqueren. Wanneer werd ingeschat dat de inflow geen probleem zou vormen ten tijde van het stenten werden patiënten ingepland voor een puur endoveneuze ingreep op de angiosuite. Uiteindelijk leidde dit tot de volgende globale verdeling; een kwart van de patiënten werd behandeld middels puur endovasculaire technieken voor IVCS, de helft werd puur endovasculair behandeld voor PTS en een kwart werd behandeld middels de hybride techniek.

De evaluatie van de uitgebreidheid van de ernst van de symptomen was relatief iets subjectiever; elke patiënt waarbij de behandelend arts inschatte dat de klachten significant genoeg waren om stenting of de hybride ingreep uit te voeren kwam in aanmerking hiervoor, met in acht neming dat er ook een anatomische obstructie was uiteraard. Over het algemeen scoorden deze patiënten hoog binnen de “Clinical, Etiological, Anatomical and Pathofysiological-classification” (CEAP-classificatie), de “venous clinical severity score” (VCSS) en de Villalta schaal. Bij al deze scoresystemen geldt hoe hoger de score hoe ernstiger de klachten. Echter was dit niet bij alle patiënten het geval. De reden hiervoor is vermoedelijk dat geen van deze scoresystemen rekening houden met de specifieke klachten van veneuze claudicatie of met de beperkingen

die een patiënt ondervindt tijdens het dagelijks functioneren. Om deze reden hebben we ervoor gekozen de genoemde scoresystemen wel te gebruiken om de uitkomst van behandeling te meten tijdens de studies, maar om deze niet mee te laten wegen bij de inclusie van patiënten.

Wat is het technische effect van stentplaatsing?

Stents worden geplaatst om bloedvaten, die eerst partieel of totaal geoccludeerd waren, open te houden. In circa 65-90% van de gevallen in onze studies werden patiënten eenmaal gestent en was daarmee de behandeling voltooid; geen secundaire interventies waren nodig en de stents bleven patent gedurende de follow-up periode (dit wordt de “primary patency” genoemd). In een aantal gevallen was een tweede interventie nodig om de stent open te houden (dus spoedige reocclusie te voorkomen), maar in deze gevallen was er dus nog nooit een reocclusie van de stents opgetreden (dit wordt de “assisted primary patency” genoemd). In deze gevallen was er sprake van een patency van 80-99% gedurende de follow-up. In een aantal andere casus was een tweede ingreep nodig om een geoccludeerde stent opnieuw open te maken (in die gevallen spreekt men van “secondary patency”). Na een dergelijke tweede interventie bleef 90-100% patent gedurende de follow-up periode.

Deze patency rates varieerden enigszins tussen de verschillende studies. Verschillen waren voornamelijk te wijten aan twee redenen: de verschillen in de lengte van follow-up tussen studies en het type ingreep dat was uitgevoerd bij een patiënt. De meeste stent reocclusies vonden plaats in het eerste jaar na stenting. Echter, waren er ook gevallen van reocclusie later tijdens de follow-up. Om deze reden is het ook logisch dat de lagere patency rates gevonden werden bij de studies met de langere follow-up tijden. Belangrijker is het verschil in patency rates tussen de verschillende behandelingen. Bij patiënten met ernstigere post-trombotische afwijkingen waren over het algemeen agressievere technieken nodig, welke geassocieerd zijn met hogere kansen op reocclusie van de stents. Dit verschil is het duidelijkst te zien tussen de patiënten die behandeld zijn voor IVCS vergeleken met PTS. Hierbij waren de resultaten bij de IVCS-patiënten beter. Een ander verschil berust op het type stent dat werd gebruikt. Toen wij onze behandelingen startten in 2009 waren enkel relatief rigide stents beschikbaar, omdat andere meer flexibele stents niet voldoende radiale kracht bezaten voor gebruik in het veneuze stelsel. Deze rigiditeit leidde tot stents die ombogen of breuken vertoonden gedurende de follow-up. Om die reden waren secundaire interventies nodig en nam de primaire patency rate af.

Specifiek van belang waren de casus waarbij er een chirurgische desobstructie van de vena femoralis communis (een endoflebectomie) nodig was in combinatie met PTA en stenting (de zogenaamde hybride techniek) en de patiënten waarbij beide benen behandeld moesten worden (unilaterale vs. bilaterale behandeling). De patency rates waren veel lager in de groep waarbij een hybride ingreep werd uitgevoerd; primary patency was 35-50%, assisted primary patency was 60-70% en secundaire patency was 70-85%. Hiervoor zijn twee belangrijke oorzaken aan te wijzen. Allereerst waren de hybride ingrepen nodig bij patiënten met de meest uitgebreide post-trombotische afwijkingen. Deze patiënten hadden om te beginnen al een veel lagere kwaliteit aan

hun veneuze systeem. Ten tweede had de endoflebectomie zelf een sterk trombogeneffect door de mate van chirurgische schade. Om deze reden hebben we er ook voor gekozen ten tijde van de ingreep een AV-fistel te creëren. Echter bleek de kans op retrombose nog steeds relatief hoog. We vermoeden dat de AV-fistel zelf een reden kan zijn geweest van de reocclusie in een aantal gevallen, daar het bekend is dat de specifieke flowcondities die de fistel creëert kunnen leiden tot lokale intimahyperplasie en stenose. En wederom had ook in deze populatie de lengte van de gemiddelde follow-upduur en het type stent dat werd gebruikt een effect op de patency rates in vergelijking met andere studies. Wanneer we de bilateraal behandelde patiënten vergelijken met de unilateraal behandelde patiënten, zien we ook een enigszins lagere patency rate. Ook bij deze patiënten was een uitgebreidere pre-interventionele veneuze schade aanwezig. Ook van belang is dat in deze patiënten veelal niet alleen de iliofemorale trajecten werden gestent, maar ook de vena cava inferior.

Verbeteren de symptomen bij patiënten?

Zoals hierboven al vermeld missen de belangrijkste scoringssystemen binnen de veneuze literatuur (CEAP-classificatie, VCSS en de Vilalta schaal) een aantal belangrijke symptomen van PTS. Doch aangezien er momenteel geen betere middelen voorhanden zijn hebben we toch gebruik gemaakt van deze scoringssystemen. Deze scores zijn gevalideerd binnen de internationale literatuur en worden frequent gebruikt bij andere studies. Om deels tegemoet te komen aan de afwezigheid van veneuze claudicatio bij deze scoringssystemen, hebben we ervoor gekozen om separaat de aan- of afwezigheid van dit symptoom te scoren bij de patiënten vóór stenting en gedurende de follow-up. Hierbij dient gezegd te worden dat deze scoring niet gevalideerd is. Om deze reden hebben we ervoor gekozen deze dataverzameling zo simpel mogelijk te houden en hebben we alleen de aan- of afwezigheid van veneuze claudicatio klachten genoteerd, er is dus geen indeling gemaakt in ernst van dit symptoom. Ook van belang is het bekende feit dat de CEAP-classificatie relatief ongevoelig is voor veranderingen in de tijd. Om die reden hebben we ervoor gekozen de CEAP-classificatie alleen te gebruiken om per studie de patiënt populatie te beschrijven, niet om veranderingen na behandeling te meten.

Over het algemeen zagen we zowel een statistisch als klinisch relevante verbetering in symptomen bij patiënten in alle follow-up studies (hoofdstuk 3-5 en 7-9). VCSS-scores verminderden over het algemeen twee tot drie punten gedurende één tot twee jaar follow-up in alle drie de verschillende behandelgroepen. Villalta scores daalden ca. 5-7 punten in diezelfde groepen gedurende de follow-up. Veneuze claudicatio verdween in ca. 70-90% van de patiënten die positief voor dit symptoom scoorden pre-interventioneel. Tussen de verschillende groepen was er geen groot verschil in puntendaling. Echter waren de baseline scores wel iets verschillend tussen de groepen; die bij de IVCS-groep waren iets lager dan bij de PTS-groep en de patiënten die een hybride ingreep nodig hadden scoorden iets hoger bij de baseline meting dan de patiënten die endovasculair behandeld zouden worden. Genezing van ulcera werd ook gescoord in de studies; de meeste ulcera genazen (ca. 80%) en de meeste daarvan recideerden vervolgens niet (wederom ca. 80%).

Verslechtering in symptomatologie, uitgedrukt als een toename in VCSS en/of Villalta score na behandeling, werd gezien in minder dan 10% van de behandelde patiënten. Dit werd het frequentst gezien in de IVCS-groep. Uit onze studies werd niet duidelijk of dit een tijdelijke of permanente stijging is. Een van de potentiële reden hiervoor kan zijn dat deze patiënten initieel gemisclassificeerd zijn als IVCS-patiënt. Het is namelijk bekend dat de compressie op de vena iliaca communis, zoals gezien wordt bij IVCS, ook aanwezig is bij een groot deel van de normale gezonde populatie. Om deze reden is het mogelijk dat mensen met een dergelijke compressie in combinatie met symptomen zoals gezien worden bij chronisch veneuze ziekte, doch met een andere oorzaak hiervoor dan de compressie, geïncubeerd zijn. Een ander punt van onduidelijkheid is de relatie tussen verlies van patency en andere complicaties. Een aantal patiënten met patente stents (met name in de IVCS groep) lieten namelijk een verslechtering in scores zien, maar aan de andere kant waren er ook patiënten met geoccludeerde stents die na een occlusie verbeterde scores lieten zien.

Een ander belangrijk feit is dat veel patiënten een lange tijd na hun (eerste) DVT-event zijn behandeld. De gemiddelde tijd tussen de eerste DVT-event en stenting/behandeling is namelijk 10 jaar en sommige patiënten zijn zelfs meerdere decennia na hun DVT pas behandeld. Dit is een belangrijk verschil met de patiënten bij wie trombolysie of een andere trombus verwijderende techniek wordt toegepast ten tijde van een acute DVT om PTS te voorkomen. Daarbij is er een nauw tijdsvenster voor de behandeling (veelal enkele weken). Ons werk laat zien dat mensen dus vele jaren na een DVT nog steeds behandeld kunnen worden indien er voldoende PTS-gerelateerde klachten aanwezig zijn en er sprake is van een anatomische obstructie in de diepe venen.

Wat zijn de nadelen van de behandeling met stents?

Globaal genomen zijn de complicaties, welke werden gezien in deze studies, als acceptabel geïnterpreteerd. PTA en stenting wordt over het algemeen goed verdragen door patiënten en de complicaties die optraden waren over het algemeen mild en tijdelijk. In alle subgroepen was er sprake van een, in intensiteit tussen patiënten verschillende, mate van pijn per- en postinterventie, met name in de lage rug. Vermoedelijk werd dit veroorzaakt door de mechanische stress die de ballon en stent op het omliggende weefsel gaven. Over het algemeen ging deze pijn vanzelf over en/of was goed behandelbaar middels NSAID's. In de casus waarbij een hybride ingreep nodig was kwamen complicaties frequenter voor en waren ernstiger, maar de meesten waren nog steeds beperkt tot de directe post-interventionele periode. In zowel de endoveneus als hybride behandelde PTS-populaties was reocclusie van de stents de meest belangrijke complicatie, zoals dit ook in de relevante wetenschappelijke literatuur beschreven wordt. Echter zagen wij in tegenstelling tot de literatuur geen stent-occlusies in de IVCS-groep. Er was wel verlies van primary patency in deze groep, dit werd echter veroorzaakt door persistente stenose na stenting. Oorzaken hiervoor waren; compressie op de stent, misplaatste stents (caudaal van de stenose) en andere typen van stent-falen. De onderliggende redenen voor patency verlies bij de PTS-behandelgroepen hangen vermoedelijk samen met problemen op de volgende drie niveaus; caudaal van de stent ofwel ter hoogte van het inflow traject, op het niveau van de

stents zelf of boven het niveau van de stents ofwel in het outflow traject. Onderdeel van de standaard behandelingsprocedure was het “landen” van de stents in gezond weefsel, dus boven en onder de post-trombotische verlittekening, dit met als doel de inflow- en outflowproblemen te minimaliseren. Op het niveau van de outflow was dit vaak relatief makkelijk te bereiken, omdat de meeste DVT's en daarmee ook de post-trombotische afwijkingen stopten op het niveau van de cavale confluens. Om deze reden was stenting van de vena cava inferior meestal ook niet nodig. Deze verlittekening liep echter vaak wel door in de vena femoralis en vena femoralis profunda, waardoor de inflow richting de stents in potentieel gevaar kwam. Dit was uiteraard in veel gevallen de reden voor het primair uitvoeren van de hybride procedure, echter bleven ook daarbij de afwijkingen in de distale vena femoralis, femoralis profunda en poplitea onbehandeld. We vermoeden dan ook dat inflow problemen de grootste invloed hadden op de patency rates in de PTS-subpopulaties. Andere belangrijke potentiële beperkingen voor de patency rates bevonden zich op het niveau van de stents zelf. Van belang waren onder andere: stent-geometrische factoren (zoals angulatie en articulatie tussen meerdere stents), inadequate antistolling (relatief laag INR bij sommige patiënten), extraluminale compressie op de stents of het endoflebectomie gebied (bijvoorbeeld door hematoom of lymfocele die frequent postoperatief ontstonden na de hybride procedure) of stenose door intimahyperplasie veroorzaakt door de AV-fistel.

Op de lange termijn waren restenose en reocclusie de enige belangrijke complicaties. Op de korte termijn was er ook sprake van een aantal complicaties gerelateerd aan de invasiviteit van de ingreep. In de puur endovasculair behandelde patiënten was de enige complicatie gerelateerd aan bloedingen; relatief kleine bloedingen kwamen voor in minder dan 10 procent van de gevallen en ernstige bloedingen in minder dan 1 procent. De belangrijkste reden voor het vóórkomen van deze complicaties was het feit dat patiënten werden behandeld onder volledige antistolling. Dit werd gedaan om de kans op stent-occlusie te verlagen, maar logischerwijs neemt de kans op bloedingen hierbij toe. In de groep die middels hybride technieken werd behandeld was het percentage bloedingscomplicaties groter (ca. 15 procent). Deze procedure werd ook onder volledige antistolling uitgevoerd, echter was het chirurgische trauma bij deze patiënten logischerwijs groter. Andere belangrijke complicaties in de hybride behandelde populatie waren: wondinfectie (ca. 30 procent), wond dehiscentie (ca. 10 procent) en lymforroe (ca. 40 procent). Deze complicaties waren over het algemeen goed behandelbaar en hadden weinig tot geen invloed op de lange termijnresultaten. Echter waren ze wel een belangrijke oorzaak voor morbiditeit op de korte termijn, verlengde ziekenhuisopname en verlengde tijd tot patiënten weer volledig mobiel waren na een ingreep.

Ook van belang is het feit dat er tijdens de follow-up geen gevallen waren van klinische longembolie en ook de mortaliteit van andere oorzaken afwezig was.

Wat kan de toekomst nog brengen?

Gedurende de tijd dat deze thesis in de maak was is de endovasculaire behandeling van IVCS en PTS langzamerhand één van de geaccepteerde behandelingsopties geworden wereldwijd en daarmee ook opgenomen in meerdere recente richtlijnen. Om deze

reden is de commerciële interesse hierin ook snel toegenomen en komen er vele nieuwe gereedschappen op de markt. Vermoedelijk is de komst van de specifieke veneuze stent de belangrijkste eerste stap geweest in de afgelopen jaren. Vermoedelijk zal het veneuze stentontwerp geleidelijk aan steeds verder verbeterd worden. Hoewel het verbeterde ontwerp van de stents logischerwijs zou moeten leiden tot betere klinische resultaten, is hier op dit moment nog geen goed wetenschappelijk bewijs voor. Directe vergelijking tussen stents zal nodig zijn, echter is het maar de vraag of een dergelijke studie in de nabije toekomst zal worden uitgevoerd.

Uiteraard zijn de meeste verbeteringen te behalen in de groep die klinisch er het slechts aan toe is. In dit geval zijn dat de patiënten met zeer uitgebreide post-trombotische afwijkingen die behandeld worden middels de hybride procedure. Omdat de geopereerde vena femoralis communis frequent stenoseert of samenvalt tijdens de (vroege) follow-up, is versteviging van dit veneuze segment een mogelijke optie om de resultaten te verbeteren. Een manier hiervoor zou zijn om ook in dat gebied een stent-achtige device achter te laten, waardoor samenvallen van het vat of dichtdrukken ervan door hematomen of lymfoceles niet meer mogelijk is. Echter zou men idealiter helemaal geen open-chirurgie meer uitvoeren en dus patiënten met zeer uitgebreide verlittekening puur endovasculair behandelen. Stenting van de distale vena femoralis communis is wellicht een waardevol alternatief en zou eventueel ook superieur kunnen zijn aan de hybride operatie. In ieder geval zou dat het vóórkomen van chirurgische complicaties sterk moeten verlagen.

De grootste winst die te behalen is ligt echter bij de preventie van PTS. Momenteel zijn een groot aantal technieken en gereedschappen, zowel chemisch als mechanisch, beschikbaar aan het komen welke gericht zijn op het verwijderen van de trombus in de acute fase. Momenteel zijn de eerste klinische resultaten hiervan helaas enigszins teleurstellend, echter zouden deze behandelingen PTS een ziekte van het verleden kunnen maken. Dit zal echter geen optie zijn voor IVCS, hiervoor zal PTA en stenting dan altijd nog nodig zijn.

VALORISATION

Yearly 1-2 in 1.000 individuals from the general population of Western countries will suffer a deep venous thrombosis (DVT). In the elderly the incidence can be as high as 1 in every 100 individuals. Up to half of DVT patients will develop the post-thrombotic syndrome (PTS). With the aging of the population as a whole, both the medical and economic impact of DVT and PTS will gravely increase. However, in both the medical world and layman media PTS is an underappreciated subject. Before the advent of deep venous stenting there was no causative treatment modality. Relatively effective symptom reduction therapy was possible in many PTS patients, mostly by use of compression garments and sometimes analgesics. However, some still suffered incapacitating symptoms, e.g. gross lower limb swelling and debilitating pain during mobilization. Moreover, many PTS patients never received this minimal level of care, and thus were undertreated. PTA and stenting in venous disease was introduced as a routine daily practice at the end of the 1990's in a number of centres worldwide, most notably in the United States of America. Since then it has slowly gained attention and implementation in more and more specialized centres worldwide. However, widespread knowledge about this treatment is still lacking in general medical daily care. This thesis is characterized by a number of unique studies, i.e. the description of the first clinical results of a specially designed dedicated venous stent (the sinus Venous stent) in chapter 4 and the first study reporting a mid-sized population treated by the combination of PTA, stenting, endophlebectomy and AV-fistula creation, offered as a standardized intervention in chapter 7. Moreover, the study in chapter 8 describing the clinical outcome of the total population of treated patients is one of the largest series available in current literature.

Therefore, this thesis adds a substantial body of data in favour of interventional treatment of PTS and IVCS. Many patients who are currently not treated for the underlying cause of their venous symptoms can benefit from PTA and stenting. As chronic treatment with medication and compression garments can be very expensive, especially in cases of venous ulceration, PTA and stenting might drastically reduce healthcare costs on the long term.

Target population in and outside the medical field

Primarily the results of PTA and stenting in chronic venous obstructive disease are of special importance to (vascular) surgeons, (interventional) radiologists, dermatologists, phlebologists, internists, geriatrists and general practitioners. Moreover, anyone in the field of medical device development, be it researchers or medical device companies, can find new targets or support for their products. A whole new field within the specialties of surgery and radiology are explored in this thesis. Also, government bodies and health insurance companies might be interested in the role of PTA and stenting in combating ever increasing healthcare costs, as this treatment may prevent the high costs from decades of conservative treatment.

Activities and implementations resulting from this thesis

The sole treatment by use of PTA and stenting has gained some attention during the last few years. However the routine use of endophlebectomy and AV-fistulas in the most severe cases of PTS is a relative novelty. Other centres worldwide might be moved to start using this treatment themselves, or find alternative ways to treat these gravely affected patients. Moreover, the use of dedicated venous stents can be implemented in many already ongoing or in new venous obstruction treatment protocols. Furthermore, these encouraging results with the first generation of dedicated venous stents can motivate medical corporations to invest in better tools, stents and other devices. However, the most important activity for the near future will be to bring the knowledge and the clinical potential of this treatment modality in the attention of the medical world as a whole.

Innovation

The most important innovation resulting from this thesis should be the improvement of care of patients suffering from deep venous pathology. Every patient suffering from PTS should have the opportunity to be evaluated by a physician knowledgeable about this subject, and if eligible be treated accordingly. Furthermore, the severity of the disease described in this thesis might add to the discussion of how DVT should be managed. As already stated many patients treated by conservative therapy for DVT (anticoagulation and compression) will develop PTS. The best management of PTS includes the prevention of PTS at the time of the initial DVT. Currently a number of thrombus removal techniques are under research, and some are already implement in specialized centres worldwide. PTA and stenting as a primary treatment might have a role in DVT prevention in IVCS patients. In their classical 1957 paper the authors May and Thurner recognized the role of the common iliac vein compression in left sided DVT pathogenesis, and indeed this was already hypothesized by Rudolf Virchow a century earlier. Treating this iliac compression, in patients who already suffer from chronic venous obstructive symptomatology, may have a profound effect in preventing DVT, and subsequent PTS development. The same can be said about the prevention of secondary DVT in PTS patient, however in these cases the thrombogenic effect of stenting itself needs to be taken into consideration.

Realisation of future activities and research

Convincing the medical world as a whole to take treatment of venous disease to the next level will be the most important aim of future research. To achieve this randomized controlled trials and great registries are needed. Development of a RCT protocol is currently taking place in our own centre. The American Venous Forum has already started a registry aimed at venous stenting in the United States of America. An European counterpart should be appropriate.

In order to improve the current treatment strategies, a number of subjects need to be studied more in-depth. Firstly, the protocol of post-interventional anticoagulation should be investigated. Currently, anticoagulation is not able to prevent a significant number of rethrombosis. Moreover, treatment might be too aggressive in a great number

of patients, especially those without a prior thrombotic event; the IVCS patients. Secondly, even though the introduction of dedicated venous stent designs has helped in attacking a number of specific stent related complications, these complications are still present after a significant number of interventions. Further improvement of stent design might be helpful in this respect. Thirdly, the use of endophlebectomy and temporary AV-fistula creation has helped us in providing a causative treatment for even those PTS patients most severely affected by post-thrombotic vein damage. However, these operations are characterized by specific complications, especially the occurrence of stenoses at the level of the treated vein and the frequently problematic wound healing. Ideally these complications can be avoided. Options might be the preventive use of VAC therapy aimed at the wound healing disorders, and the use of special intra-operatively deployable inlays for the endophlebecomized common femoral vein.

In conclusion it can be stated that the world of deep venous reconstructions is still in its infancy. Much efforts will be needed to reach the next stage, but this has the potential to revolutionize the field of vein disease.

DANKWOORD

De kwaliteit van de hedendaagse medische zorg staat of valt met de kwaliteit van de samenwerking van haar uitvoerders. Voor promoveren binnen de geneeskunde geldt hetzelfde. Terugkijkend op de afgelopen zeven jaar kan ik dan ook niet anders dan concluderen dat de realisatie van dit proefschrift mogelijk is gemaakt door de samenwerkingsrelaties, of andersoortige verbindingen, met een groot aantal personen.

Prof. dr. Wittens, beste Cees, getipt door Rob schreef ik je een sollicitatiebrief. Je nodigde me uit voor een gesprek en vroeg me direct waarom ik tegenover je zat. Ik antwoordde dat ik over 10 jaar een gepromoveerde vaatchirurg wilde zijn. “Gaan we regelen” zei je, einde sollicitatie gesprek. Je nam me aan en ging over tot de orde van de dag. De volgende 6 jaar zou een achtbaan van belevenissen en ervaringen blijken; code rood deadlines werden afgewisseld met reizen naar buitenlandse congressen, marathonpoli's tot diep in de nacht werden afgewisseld met feestjes in jouw achtertuin. De druk was soms hoog en wat je vroeg was soms veel, maar uiteindelijk werd ik van dit alles een betere wetenschapper, arts en persoon. Terugkijkend op deze periode ben ik het meest dankbaar voor alle kansen die je me gaf; de artikelen waarvoor jij was gevraagd die we samen schreven, de mogelijkheid om voordrachten op congressen binnen en buiten Europa te geven, het leren echoën en natuurlijk het Amsterdamse avontuur. Daarnaast waren Irma en jij ook buiten het ziekenhuis altijd zeer gastvrij.

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Rob, letterlijk op dag één van ons eerste collegejaar geneeskunde leerden we elkaar kennen. Samen hebben we de facultaire introductie doorlopen. Het toeval verlangde dat we ook de eerste onderwijsgroepen samen zouden doorlopen. Later beiden actief bij studievereniging Reflex, op een blauwe maandag in maart nog eens een herendispuut opgericht met een aantal gelijkgezinden, om vervolgens beiden voor de chirurgie te kiezen in ons laatste jaar geneeskunde. Van toeval was toen geen sprake meer. Zeker niet toen we beiden bij Cees begonnen. Vele congressen, “zakenreizen” en co-publicaties

verder koos jij er als eerste voor uit het chirurgische avontuur te stappen. Een keuze die de hele boyband later nog zou maken. Daarnaast zakte je door een door de liefde ingegeven migratie drang verder de Maas af. Ik zou uiteindelijk volgen om diezelfde reden. Het lot wilde dat je terug zou keren, uiteindelijk maar tijdelijk, naar de praktijk van Cees. Maar ten tijde van dit schrijven ga je weer een nieuw hoofdstuk in je leven in.

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Irwin, jij was al jaren eerder bekeerd door Cees. Vanaf de eerste avondpoli was duidelijk dat MRV weliswaar beter reproduceerbaar was dan echografie, maar in kwaliteit toch soms het onderspit moest delven. Dit alles had natuurlijk te maken met de bekende "operator dependency" van de duplex sonografie. Gedurende mijn jaren in het MUMC+ en later in Amsterdam, was jij altijd bereid tot ondersteuning in de kliniek en wetenschap en stond je ons bij met gevraagd en ongevraagd commentaar. Maar ook voor whisky en sigaren in Oost-Europa draaide jij je hand niet voor om. Mijn dank voor jouw enorme aandeel in de dataverzameling en de kritische blik op de artikelen, maar bovenal voor het mij wegwijs maken in de wereld van de echografie, vaardigheden die ik nu dagelijks nodig heb.

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tijdens MDO's en researchvergaderingen heeft een duidelijke stempel gedrukt op de planning en analyses van de studies. Ook jij verkoos een toekomst buiten de chirurgie, maar nog wel binnen de flebologie. En ook jij zocht deze toekomst in het Rotterdamse.

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CURRICULUM VITAE

Mark Antonius Friedrich de Wolf werd op 24 maart 1985 geboren te Deurne, Noord-Brabant. Tussen 1998 en 2004 volgde hij zijn middelbare schoolopleiding aan het Peelland College Deurne, waaraan hij diploma's op atheneum niveau behaalde in een tweetal profielen. Aansluitend startte hij zijn geneeskunde opleiding aan de Universiteit Maastricht, waaraan hij in 2010 afstudeerde als arts.

Hierop volgend startte hij zijn promotieonderzoek, bij diezelfde universiteit, onder supervisie van zijn promotor prof. dr. Cees Wittens en copromotor dr. Rick de Graaf. Zijn onderzoek is gericht op de uitkomst van diep veneuze reconstructies bij patiënten met chronisch veneuze ziekte. In 2013 switchte hij naar een klinische positie als arts-assistent bij diezelfde afdeling veneuze chirurgie van het Maastricht universitair medisch centrum, hierbij zette hij zijn promotieonderzoek voort. In 2015 maakte hij de stap richting de Nederlandse hoofdstad om als arts te werken bij een nieuw opgezette kliniek gespecialiseerd in de behandeling van diep veneuze pathologie. Dit proefschrift is het resultaat van de research die hij gedurende zijn werkzaamheden bij deze afdelingen heeft ondernomen. Vanaf 1 mei 2016 is hij gestart aan de opleiding tot radioloog in het Maasstad ziekenhuis te Rotterdam (opleider dr. D. Vroegindeweyj).