Enhancing Cure and Care for Patients with Chronic Venous Disease

Bram Rook

RADBOUD UNIVERSITY PRESS

Radboud Dissertation Series

Enhancing Cure and Care for Patients with Chronic Venous Disease

Bram Rook

Financial support for printing this thesis was kindly provided by the Department of Dermatology of the Radboud University Medical Centre and Wijngaarden Medical BV.

The studies described in this thesis were conducted at Ziekenhuis Groep Twente, Deventer Ziekenhuis and the Erasmus Medical Centre.

Enhancing Cure and Care for Patients with Chronic Venous Disease
Bram Rook

Radboud Dissertation Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Proefschrift AIO | Guntra Laivacuma
Printing: DPN Rikken/Pumbo

ISBN: 9789465152035
DOI: 10.54195/9789465152035
Free download at: https://doi.org/10.54195/9789465152035

RADBOUD
UNIVERSITY
PRESS

Enhancing Cure and Care for Patients with Chronic Venous Disease

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens het besluit van het college van promoties
in het openbaar te verdedigen op

woensdag 14 januari 2026
om 16:30 uur precies

door

Bram Rook
geboren op 9 december 1992
te Zwolle

Promotor
Prof. dr. E.M.G.J. de Jong

Copromotoren
Dr. E.B.M. Kroft, Kliniek Twente
Dr. M.J.E. van Tongerlo - van Rijn, Erasmus MC

Manuscriptcommissie
Prof. dr. D. Ulrich
Prof. dr. T.E.C. Nijsten, Erasmus Universiteit Rotterdam
Dr. C.J.M. van der Vleuten

Paranimfen
Dr. B. Koopman
Drs. L.J. de Vries

Table of contents

Chapter 1
General introduction 9

PART ONE
Comprehensive treatment and follow-up care during and after visit to the one-stop clinic for venous leg ulcers

Chapter 2
Evaluation of the introduction of the one-stop clinic and dedicated nurses for venous leg ulcer care in the East of the Netherlands 31

Chapter 3
Quality of life of patients with venous leg ulcer treated by a one-stop clinic 55

Chapter 4
The first comparative study of financial costs of treatment of venous ulcers at a Dermatology one-stop clinic followed up by specialized nurses in the community compared to 'standard care': A prospective pilot study 73

PART TWO
Treatment and prevention of post-thrombotic syndrome

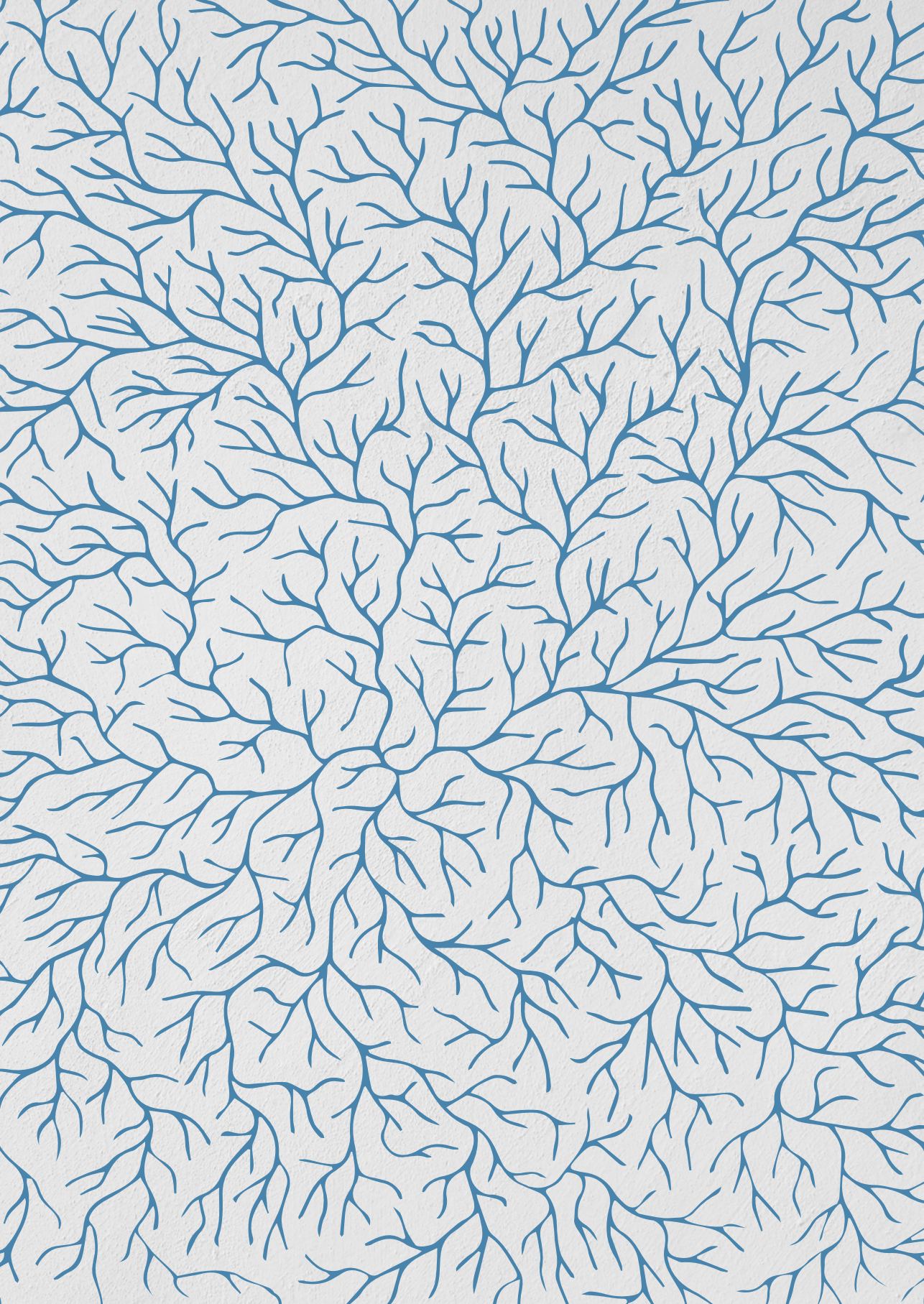
Chapter 5
The value of compression therapy following deep venous thrombosis 91

Chapter 6
Effect of exercise after a deep venous thrombosis: a systematic review 107

Chapter 7
Feasibility of a treadmill test in patients with venous claudication in the work-up of endovenous stenting 135

Chapter 8
General discussion 151

APPENDIX 169



Chapter 1

General introduction

GENERAL INTRODUCTION

Characteristics of chronic venous diseases

Chronic venous disease (CVD) belongs to the most common non-infectious diseases worldwide.[1–3] The incidence is expected to increase significantly with a worldwide aging population. It is a chronic and debilitating condition that can dramatically impact a patient's life, physically and mentally, and their productivity.[3] Furthermore, CVD is taking up an increasing share of Western healthcare systems and their budgets.[4,5] Many factors play a role in the course of this condition and are therefore a potential target for prevention and therapeutic strategies. Despite the chronic nature of the disease and its high burden, there are still few therapeutic options to stop diseases progression or even improve its symptoms. Therapeutic options still mainly consist of conservative measures (compression and lifestyle interventions), pharmaceutical therapy and patient specific invasive therapy. However, today, healthcare outcomes are increasingly patient-centred and focused on quality of life (QOL). In addition, due to the further digitalization of society, there might be more options to tailor preventive strategies of treatment therapies and further improve the care for CVD patients. This thesis addresses several of these preventive or treatment modalities to further improving the care of CVD. However, before we can explore new treatment strategies, we must first understand the disease itself.

CVD is multifactorial and its clinical manifestation ranges from mild forms, such as itching or cramps, to severe ones such as venous leg ulcers (VLUs).[6] It consists of a spectrum of venous diseases of different causes that can occur after damage to both superficial and deep veins throughout the body, most often in the legs.[2,7] It is estimated that deep venous diseases account for approximately 40% of all VLUs.[8] Although the data are scarce, these deep venous disease-related VLU are thought to have higher recurrence rates and a substantial economic burden. The veins can be damaged by different events, which has a negative impact on the flow of blood back to the heart. When damaged veins cannot pump the blood adequately to the heart, the blood will pool. When this leads to edema it is called chronic venous insufficiency (CVI).[9] All of the veins in the legs, arms and abdomen can be affected.[1,6] CVI can lead to a cascade of tissue changes that subsequently lead to symptoms and clinical signs. A known very common venous disease is varicose veins (VVs), which in time can progress to CVI.[2] Another important and common venous disease is an acute deep vein thrombosis (DVT). The feared long-term complication of DVT is post-thrombotic syndrome (PTS).[10] PTS has a spectrum of clinical manifestations, ranging from localised itching to chronic wounds of the limbs, most often involving

the legs. PTS is the most common complication of a prior DVT, despite primary prevention such as prophylactic exercise recommendations and anticoagulation use and secondary prevention like compression therapy after an acute DVT.[11] The syndrome can develop within two years after DVT, but can also manifest later in life.

Pathophysiological mechanisms of symptomatic CVD

In the vascular system of the body, the pressure on the arterial side is high due to cardiac output and vascular resistance, which creates an optimal perfusion state in the tissues. As a result, all tissues are receiving their nutrients and oxygen, while waste products and carbon dioxide can be disposed. On the venous side, intravascular pressure is significantly lower and the deoxygenated blood is transported back to the heart.[1,12] The venous system can anatomically be divided in superficial and deep veins, as well as perforating veins, the latter connecting superficial and deep veins. To overcome gravity for venous blood to be flowing back to the heart, especially from the extremities and abdomen, veins contain one-way valves. These valves prevent backflow, or reflux, of blood and limits pooling of the blood in the extremities, while muscle contractions especially of the calf, the gastrocnemius and soleus muscles, 'pump' the blood back to the heart.[13]

All types of veins can be damaged individually, or there might be a combination of different affected types and segments. Various factors can lead to incompetent veins and, through a complex cascade, to CVD. The disease is often categorized as congenital, primary and secondary CVD. Congenital CVD includes conditions that already are present at birth or manifest later in life. Primary CVD is defined as a degenerative process of the venous valve and/or venous wall that leads to a decrease in strength and pathological reflux without an explicit cause.[14] This process is believed to be initiated by inflammatory processes in the veins and their surroundings.[12,15] Risk factors include older age, genetics, female sex, obesity, low physical activity, prolonged standing and sedentary occupation.[2,16] Secondary CVD is caused by extravenous factors, such as extrinsic compression, or intravenous factors, most commonly DVT. Damage to the valves, for example due to a thrombus, can lead to reflux, or backflow, of blood. This valvular reflux compromises the normal flow of blood from the legs or arms to the heart and subsequently leads to higher venous intravascular pressure in the acute phase, known as venous hypertension. In case of thrombosis, the thrombotic vein may recanalize, but often this is incomplete, continuing the venous obstruction.[17] During the recanalization in the chronic phase the thrombus can be resolved. In case of damage, due to a thrombus or other cause, a local inflammatory reaction occurs as part of the healing process that can lead to scar tissue in the veins, known as trabeculation.

If this becomes severe, with or without a combination of residual thrombus, there will be more resistance and reflux that contributes or leads to venous hypertension in the chronic phase. Most often this problem involves the legs, but it can also occur in the upper extremities and abdominal veins. Venous hypertension increases the capillary hydrostatic pressure causing extracellular edema due to excessive filtration.[17] In case of primary CVD, impairment of surrounding and mural connective tissues such as elastin and collagen in the veins leads to failure of venous valve closure and is thought to be the primary defect that lead to VVs and subsequently to venous hypertension.[1,17] Examples of congenital CVD are veins that may not have been formed or developed properly or malformations that do not function optimally.[14] Over time, venous hypertension leads to CVI, which is a state of continuous restriction of venous blood flow causing edema. This chronic change of the microcirculation leads to cellular and tissue damages which can eventually to venous symptoms.[12,13,15,17] The pathogenesis of both primary and secondary CVD until symptoms occur is a complex cascade.[1,6,12,13,15,17] Multiple theories try to explain this pathogenesis, including precapillary fibrin cuff formation leading to hypoxia in tissue, white blood cell trapping activating inflammatory processes and trapping of fibroblasts, endothelial cells, and keratinocytes which inhibit the growth process.[1,6]

Epidemiology

CVD is a condition that is very common and the incidence is anticipated to increase significantly with an aging population. This is due to medical advances with a longer expected lifespan.[3,9,18] The prevalence varies widely by geographic location though it is the highest in countries in high income countries.[19] Prevalence rates of CVD vary from <1% to 40% in females and from <1% to 17% in males, depending on the distribution of potential risk factors, such as older age, obesity, low physical activity and standing occupations.[2] The exact prevalence rates are difficult to establish since CVD tends to be under-recognised.[3] In the Vein Consult program cohort, it was stated that general practitioners (GPs) considered only 51% of all patients with a low score on the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification (table 1) to have CVD, leaving almost half of the patients undiagnosed.[14,19] Moreover, there is a poor correlation between venous symptoms and signs indicated by patients and symptoms and signs seen during investigation.[20] It is not always clear without further investigation what the underlying pathophysiology is, since different pathologies can lead to similar symptoms and clinical venous signs.[20,21] The clinical presentations of CVD using the CEAP classification that have the highest prevalence internationally are telangiectasia (C1, 26%) and VVs (C2, 19%).[3] The same study found that at follow-up of 13.4 years, almost 32% of patients were estimated to have CVD progression from the initial diagnosis, with 22% of patients

Table 1. The 2020 update of the CEAP classification[27]

Class	Description
Clinical (C) class	
C0	No visible or palpable signs of venous disease
C1	Telangiectasia or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to CVD
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed ulcer
C6	Active venous ulcer
C6r	Recurrent venous ulceration
Symptomatic or not: subscript 'S' or subscript 'A'	S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction A: asymptomatic
Etiological (E) class	
Ep	Primary
Es	Secondary
Esi	Secondary – intravenous
Ese	Secondary – extravenous
Ec	Congenital
En	None identified
Anatomical (A) class	
As	Superficial
Ad	Deep
Ap	Perforators
An	No identifiable venous location
Pathophysiological (P) class*	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No pathophysiology identified

* Reporting of pathophysiological class must be accompanied by the relevant anatomical location. CEAP=Clinical, Etiological, Anatomical, Pathophysiological. CVD = chronic venous disease

progressing to having a VLU in 6 years.[3] The most serious clinical presentation of CVD, including PTS, are VLUs. Prevalence of an active VLU is estimated at 0.4%.[3] Before the age of 45 years, the condition is rare, with an incidence ranging between 0.73–3.12 per 1000 person-years.[8,22,23] Again, with increasing age, the incidence of VLUs increases; in patients aged 75 years or older, the incidence is 8.3 per 1000 patient-years among women and 2.2 per 1000 patient-years among men.[24] The risk of recurrence of VLUs can be high, with a rate of 57% within the first year.[8]

True demographics of CVD and of its underlying causes is difficult to establish due to both the difficulty to diagnose CVD, but also to defining it. Incidence of CVD is often investigated using clinical scoring systems, such as the Clinical class of the CEAP classification, thus using the phenotype and the clinical stage and not the etiology. However, it is known that the most common cause of CVD is the primary type (Ep in the CEAP classification, table 1) defined as a degenerative process of the venous valve and/or venous wall.[14] The next most common manifestation of CVD is PTS(3). This syndrome occurs in 20–50% of all DVT patients, of which 5–10% develop severe PTS, including VLUs.[25,26] PTS usually occurs in the first years after DVT, but may develop even after 10–20 years.[8,21-23]

Impact on quality of life

Symptoms of CVD can have a significant impact on the QOL such as psychosocial wellbeing and social functioning.[28,29] Besides leg symptoms such as pain and itching, sleep deprivation, social isolation, reduced mobility and smell can occur, leading to lower selfesteem and reduced vitality. The QOL of patients with VLU is estimated to be similar of patients with congestive heart failure.[5] Guidelines have long focused on the prevention and healing of VLUs, though patient-centred outcomes such as pain, social functioning and QOL in all CVD patients were underestimated, resulting in limited available information and data on how to organise ulcer care in a practical, patient-centred way.[29,30] Since CVD care is slowly drifting towards more value-based care, patient-reported outcome measures (PROMs) are increasingly important.[16,31,32] To improve health status of patients, healthcare professionals' awareness of the overall impact of CVD should increase, and knowledge and evaluation of QOL assessment and organizing optimal care should receive more attention. Evaluating both patients' and healthcare workers' preferences and experiences regarding CVD care could provide insights to further improve patient-centred outcomes and contribute to more value-based care.[31]

Economic burden

Since CVD is so widespread and its prevalence is expected to increase significantly, the economic burden is substantial.[8] In 2010, the care and treatment of CVD was estimated to be 2% of national healthcare budgets of developed countries.[33] The disease imposes a high burden on the healthcare system due to high direct and indirect medical costs, lost productivity or even loss of employment. Only for VLU the annual direct medical costs are estimated to be $5527 USD per person per year.[8] Establishing a quick and correct diagnosis and initiating proper treatment may result in a shorter time of wound healing, and restoring of QOL.[21] Simultaneously, a cost reduction is expected.[34,35] Early interventions of underlying CVD have shown to be cost-effective.[16,36–39] This substantial economic burden emphasises the importance of accurate and early initial diagnosis, initiating of a tailored treatment and monitoring the healing process closely by skilled healthcare professionals to prevent disease progression or expensive hospital admissions.

Diagnosis and classification of post-thrombotic syndrome and venous leg ulcers

Post-thrombotic syndrome

In the event of a previous DVT, signs and symptoms of CVD are considered as PTS.[26] The diagnosis of PTS is based on clinical symptoms and signs that can be observed during physical examination. Symptoms vary from having a feeling of tired heavy legs after standing or walking up to pain, cramps, itching and/or paraesthesia. During physical examination there might be a difference in size between both legs and signs of CVI can be observed, consisting of edema, eczema, VVs or different skin alterations.[40] Venous claudication (VC) can also be reported by patients. This is a tense or discomfort feeling in the leg or severe pain when walking or standing. Symptoms and signs of PTS are on a wide scale, where there does not exists a step-by-step order of sequence. Symptoms might be persistent or intermittent. The severity might even change over the course of the day.

Due to the various and often intermittent clinical manifestations, it is challenging for both physicians and researchers to establish an optimal definition of PTS.[11,41] There is no 'gold standard' for its diagnosis which impairs comparison between research studies. Due to the wide range of clinical characteristics, PTS is often scored based on a cumulation of symptoms and clinical signs observed during physical examinations. Using too low a threshold causes overdiagnosis, leading to overtreatment, which places an extra burden on patients and results in excessive medical costs. On the other hand, underdiagnosing might lead to underestimating

the disease and undertreatment and if venous insufficiency is not treated appropriately, it may increase disease severity over time.

Scoring systems are used both to determine the diagnosis and the severity of the disease. This may mean that one tool might be better as a screening tool and others as a tool to evaluate disease severity over time. Scoring instruments that are used to diagnose and classify PTS are often scoring systems that are designed to investigate general CVD. Examples are the CEAP-classification (table 1) and the (revised) Venous Clinical Severity Score (VCSS).[25,27,42] The ability of these instruments to diagnose PTS is limited, since often there are no clear definitions and cut-off values for the diagnosis and the tests are not validated for specific PTS populations. Currently, more disease-specific measurement instruments are used.[27] The International Society on Thrombosis and Haemostasis recommended the Villalta-scale as the standard to diagnose and classify severity of PTS, due to its properties such as utility, low interobserver variability, validity, and ability to monitor treatment.[25,43–45]

Table 2. The Villalta scoring system[44]

score-item	**score***			
symptom	**absence**	**mild**	**moderate**	**severe**
pain	0	1	2	3
cramps	0	1	2	3
heaviness	0	1	2	3
paraesthesia	0	1	2	3
pruritus	0	1	2	3
clinical signs				
pretibial edema	0	1	2	3
skin induration	0	1	2	3
hyperpigmentation	0	1	2	3
erythema	0	1	2	3
venous ectasia	0	1	2	3
pain on calf compression	0	1	2	3

PTS = post-thrombotic syndrome
* Each item is scored as 0 (absence), 1 (mild), 2 (moderate) or 3 (severe).
Total score 0-4: no PTS; 5-14: mild to moderate PTS; > 14: severe PTS.
Presence of venous ulcer automatically confers the highest severity (severe).

However, the Villalta-scale lacks the ability to monitor the impact on QOL during treatment.[31] In a common chronic disease such as PTS, especially in the presence of a VLU, patient-oriented outcomes such as QOL are important to consider, since due to the nature of the disease it can impair QOL dramatically. Knowledge of factors responsible for a decreased QOL may help healthcare workers to improve CVD management and patient-centred outcomes. QOL assessments may result in information that can be used to improve therapy plans for patients. Moreover, it can result in improved communication between patients and healthcare workers. Though it is suggested that the Villalta score is correlated with QOL, validated QOL questionnaires, specifically focusing on the long term effects of PTS or VLU patients, are still missing. Recently, only two questionnaires were identified to consider in patients with CVD.[31] Such health-related quality of life (HRQOL) questionnaires are important to identify patients suffering from PTS, but also to evaluate treatment effects, establishing benchmarks to decrease variability in care and compare outcomes between studies.

Venous leg ulcers as end stage of chronic venous insufficiency

At the severe end of the spectrum of clinical manifestations of CVD, the occurrence of a VLU is a serious and debilitating complication that can develop spontaneously or after minor trauma. This can occur due to both superficial and deep venous diseases, the first accounting for most VLUs.[8] Often, a VLU is the initial presentation of CVD, while other CVD-related symptoms may have been present for a longer period.[46] The prevalence of all lower leg ulcers in the general population is estimated at 1% and increases up to 4-5% among individuals above 80 years.[46–48] The majority of all lower limb ulcers are caused by venous diseases and VLUs represent approximately 70% of all lower leg ulcers.[46,47,49] The overall number of patients with a VLU increases because of increasing life expectancy and obesity rates.[48]

Of all patients with DVT, 10% eventually develops severe PTS, which often, depending of the definitions, include VLUs. The risk of developing a VLU increases with the duration of PTS.[50] Five percent of patients may develop ulcers 10 years after a prior DVT.[51] Although VLUs are debilitating, painful and can significantly reduce patients' QOL, ulcer healing has been shown to restore QOL.[52] VLUs are typically long-lasting and the percentage that heal at 12 weeks is 44.1%, increasing to 80.0% within two years, while around 8.0% of ulcers remain unhealed after five years.[22,53]

In addition to diagnosing and determining the severity of CVD, examinations are necessary to exclude other etiologies and are used to consider treatment options. Vascular examinations, such as measuring the ankle-brachial pressure index (ABPI)

and toe-brachial index (TBI), or performing a duplex ultrasound, can distinguish between an arterial and venous cause of the symptoms.[46] Duplex ultrasound is the gold standard for accurate evaluation of the highest point of valve incompetence and sites or reflux, to assess the presence and extent of venous insufficiency.[1,13] Additionally, duplex ultrasound is used to assess whether the venous insufficiency is caused by obstruction or valve incompetence, especially when considering invasive treatment. Less often, histopathological examination of the skin and ulceration is indicated, which could lead to a diagnosis of inflammation or malignancy. Establishing a quick and accurate diagnosis is essential to improve outcomes. If a proper treatment can be initiated swiftly, there will be a shorter time of wound healing in addition to an increased QOL and reduction of economic costs. Therefore, a multidisciplinary approach of ulcer care is vital.

Therapeutic management

There are different therapeutic approaches to address CVD. Therapy can be divided into acute management of diseases such as an acute DVT to prevent CVD, symptomatic treatment, and prevention of progression of disease severity. Furthermore, therapy of CVD consists of three major groups: conservative treatment, pharmaceutical therapy and invasive interventions.

Conservativetreatment options

Compression The cornerstone of treatment for CVD has long been compression therapy and this still remains an important therapeutic option.[9,16,28,54] Through external compression, the interstitial pressure increases, which in turn decreases intravenous pressure and reduces valvular reflux by improving the venous pump function of the calf and decreasing edema.[54] VLUs heal more quickly and have a lower recurrence rate when treated with effective compression therapy.[16,25,55] Compression therapy can both relieve symptoms and reduce the risk of disease progression, although non-compliance occurs frequently.[56,57]

Research on the most effective compression therapy demonstrated that multi-layer compression and elastic compression are superior compared to single layer or inelastic compression.[25,58] Previously, all patients with DVT were advised to wear compression stockings for at least two years to prevent CVD (specifically PTS).[56] However, tailoring compression therapy to individual patients has been shown to reduce costs and may increase compliance.[56,59–61]

Lifestyle interventions There is a growing focus on lifestyle interventions for CVD patients.[16,25,62,63] Lifestyle interventions benefit CVD outcomes such as healing rates

or reduction in symptom severity.[25,52,64] Current interventions focus on exercise therapy, weight-reducing therapies or behavioural changes such as avoiding prolonged standing.[65,66] However, such interventions might require a more self-managed strategy where patients participate in their own treatment process. Particularly as CVD care shifts to a more patient-centred approach and value-based care, social and psychological factors are more significant. This is especially true because CVD and VLUs have a considerable impact on QOL and social and psychological impairment have been associated with delayed healing of VLUs.[67] Extensive counselling of patients about their disease can therefore increase compliance and stimulate patient empowerment and involvement. There is still a knowledge gap on which type of interventions are best applied to this patient group and how optimal treatment compliance is achieved and maintained in the longer term. However, the increasing availability of tracking devices can make these types of interventions more accessible and accelerate research in the near future.[62,66]

Pharmaceutical therapy

Another therapeutic option consists of pharmaceutical interventions. In case of a previous DVT, often patients require anticoagulation to help clear the thrombus or clot and decrease the risk of recurrence or residual thrombosis in the longer term and prevent complications such as pulmonary embolisms.[56,68] Especially in patients without non-modified risk factors for DVT, anticoagulation therapy might be advised for lifetime use.[56] Wound treatment is vital in case of VLUs and pharmaceutical options are often used in wound treatment. Most of all, early identification of a VLU is crucial to initiate therapy early and evaluate if further diagnostic testing is necessary, while in some cases invasive interventions might be indicated. Some VLU patients present with infected ulcers, whereas in other cases, the VLU is infected during treatment. Infected VLUs can delay ulcer healing, increase health care costs and lower QOL.[69] Therefore, infections need to be prevented, or when they do occur, aggressive antibiotic treatment is required.[34,69–71] Veno-active agents can be used as another pharmacological treatment in CVD to treat symptoms as pain or edema, although treating the cause of venous reflux and venous hypertension should be prioritized. Pain can be treated by systemic pain medication, for example non-steroid anti-inflammatory drugs(NSAIDs). Local pain treatment includes application of topical eutectic mixture of local anaesthetics (EMLA) (lidocaine-prilocaine cream) or NSAID dressings.[72] Another potential therapeutic option is the usage of specific wound dressings that might improve the wound environment, aiming for faster wound healing. However, robust scientific evidence for this latter intervention lacks.[73,74]

Invasive interventions

The aim of invasive therapy can be to treat superficial venous incompetence or deep venous pathology.[16] Often, the indication for treatment of superficial venous incompetence is based on duplex ultrasound findings, patient preference, the expected impact on QOL, the estimated risk of deterioration of CVD, and the local availability of interventional options. Invasive treatment for symptomatic VVs is recommended and cost-effective, with increasing use of minimally invasive options such as endovenous techniques, including thermal or radiofrequency ablation, non-thermal ablation (sclerotherapy), or more classic interventions such as ligation, stripping, and phlebectomies.[9,16]

Disease states that are eligible for deep venous interventions include acute DVTs, moderate to severe PTS, VC and resistant or recurrent VLUs.[16,28,56,75] In an acute iliofemoral DVT, early endovascular thrombus removal techniques were shown to significantly reduce the risk of PTS, especially moderate to severe PTS, compared to anticoagulation alone.[56] However for most CVD, invasive options are only considered when conservative and pharmaceutical treatment options have failed.[16,28,75] Venoplasty procedure in combination with stenting is most commonly performed in case of caval and/or iliofemoral obstruction.[16] In these cases, the obstructed part of the vein is widened with a balloon and subsequently a stent is placed. Extension of the stent rarely surpasses the confluence of the femoral vein and the deep femoral veins. Open surgery is rarely performed. In the acute DVT setting, patients with severe symptoms and a caval and/or iliofemoral thrombus may be considered for early clot removal in order to prevent damage to the veins.[56]

Research questions and thesis outline

Among patients with CVD, VLUs frequently occur as a long term complication of different underlying etiologies. Sometimes, a VLU is the first presentation of CVD. VLUs are the most invalidating complication of CVD and are therefore considered to be its end stage, with a high impact on QOL and a large economic burden. As the total number of patients with CVD increases due to a growing and changing population with longer life expectancy and improved welfare, the long-term impact of CVD and its complications, such as VLUs, becomes even more challenging.[3,5,18] This thesis aims to contribute to two different aspects of CVD. The first aspect is the optimization of the current work-up of leg ulcer patients with a patient-oriented approach. This led to the following research question:

Does an efficient, evidence-based healthcare system result in improved patient-centred outcomes for VLU care?

The first part of this thesis aims to evaluate the efficacy of the one-stop clinic, an efficient, evidence-based, integral system of venous ulcer care. Chapter 2 focuses on the effect of this one-stop clinic and the introduction of a dedicated nursing team for the follow-up of patients with a VLU. The aim of the chapter was to investigate whether this set-up led to faster wound healing rates due to early recognition of the underlying pathology of leg ulcers and rapid initiation of the most optimal treatment approach. Furthermore, we assess whether this method had a positive impact on QOL (Chapter 3) and costs (Chapter 4). The study results could contribute to a more protocolized set-up of ulcer care nationwide, with more attention to patient-oriented outcomes.

In the second part this thesis further focuses on specific promising preventive, diagnostic and therapeutic options for CVD, in particular CVD caused by a previous acute DVT, or PTS. In the current digital era new and more individualized modalities are on the rise that could contribute to current CVD care. Moreover, the increasing economic healthcare costs forces researchers and physicians to critically assess evidenced-based healthcare. This led to our second research question:

Does optimizing the diagnostic process and conservative treatment options enhance the effectiveness of PTS care?

First, in Chapter 5, this thesis evaluates the literature on the effect of compression therapy, as there is a shift to a more individualized approach in recent years. Chapter 6 describes whether exercise training might be a potential therapeutic target to improve outcomes of CVD, especially among PTS patients. Further, in Chapter 7 a study is described that evaluates whether symptoms of VC could be quantified using a treadmill test in the work-up of venous stenting. With this information, we hope to assess and understand patients' symptoms better and correlate differences in treadmill parameters with an objective improvement in symptom-free walking distance after venous stenting, and subsequently assess the effectiveness of stenting. Finally, in the discussion in Chapter 8 we discuss all the results of the studies and we discuss future perspectives of CVD care.

REFERENCES

1. Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F, et al. Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *J Clin Med.* 2021 Jul 22;10(15):3239.
2. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol.* 2005 Mar;15(3):175-84.
3. Salim S, Machin M, Patterson BO, Onida S, Davies AH. Epidemiology of Chronic Venous Disease: A Systematic Review With Pooled Prevalence Analysis. *Ann Surg.* 2021 Dec 1;274(6):971-976.
4. Kim Y, Png CYM, Sumpio BJ, DeCarlo CS, Dua A. Defining the human and health care costs of chronic venous insufficiency. *Semin Vasc Surg.* 2021 Mar;34(1):59-64.
5. Onida S, Davies AH. Predicted burden of venous disease. *Phlebology*. 2016 Mar;31(1 Suppl):74-9
6. Ligi D, Croce L, Mannello F. Chronic venous disorders: The Dangerous, the Good, and the Diverse. *Int J Mol Sci*. 2018 Aug 28;19(9):2544.
7. Jacobs BN, Andraska EA, Obi AT, Wakefield TW. Pathophysiology of varicose veins. *J Vasc Surg Venous Lymphat Disord.* 2017 May;5(3):460-467.
8. Kolluri R, Lugli M, Villalba L, Varcoe R, Maleti O, Gallardo F, et al. An estimate of the economic burden of venous leg ulcers associated with deep venous disease. *Vasc Med.* 2022 Feb;27(1):63-72.
9. Azar J, Rao A, Oropallo A. Chronic venous insufficiency: a comprehensive review of management. *J Wound Care.* 2022 Jun 2;31(6):510-519.
10. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res.* 2018 Apr;164:100-109.
11. Baldwin MJ, Moore HM, Rudarakanchana N, Gohel M, Davies AH. Post-thrombotic syndrome: a clinical review. *J Thromb Haemost*. 2013 May;11(5):795-805.
12. Raffetto JD. Pathophysiology of Chronic Venous Disease and Venous Ulcers. *Surg Clin North Am*. 2018 Apr;98(2):337-347.
13. Meissner MH, Moneta G, Burnand K, Gloviczki P, Lohr JM, Lurie F, et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg.* 2007 Dec;46 Suppl S:4S-24S.
14. Lurie F, Passman M, Meisner M, Dalsing M, Masuda E, Welch H, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord.* 2020 May;8(3):342-352.
15. Castro-Ferreira R, Cardoso R, Leite-Moreira A, Mansilha A. The Role of Endothelial Dysfunction and Inflammation in Chronic Venous Disease. *Ann Vasc Surg.* 2018 Jan;46:380-393.
16. De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg.* 2022 Feb;63(2):184-267.
17. Bradbury AW. Pathophysiology and Principles of Management of Varicose Veins. In: Fitridge R, Thompson M, editors. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists [Internet]. Adelaide (AU): University of Adelaide Press; 2011. 24. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534256/ [accessed 8 February 2024].
18. Davies AH. The Seriousness of Chronic Venous Disease: A Review of Real-World Evidence. *Adv Ther.* 2019 Mar;36(Suppl 1):5-12.

19. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F; VCP Coordinators. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. *Int Angiol. 2012* Apr;31(2):105-15.
20. Perrin M, Eklof B, Van Rij A, Labropoulos N, Vasquez M, Nicolaides A, et al. Venous symptoms: the SYM Vein Consensus statement developed under the auspices of the European Venous Forum. *Int Angiol.* 2016 Aug;35(4):374-98.
21. Nicolaides A, Kakkos SK, Estrada-Guerrero JG. Chronic venous disease: What if everything started with early care? A discussion with experts. *Phlebology*. 2024 Sep;39(8):509-511
22. Nelson EA, Adderley U. Nelson EA, Adderley U. Venous leg ulcers. *BMJ Clin Evid.* 2016 Jan 15;2016:1902.
23. Berenguer Pérez M, López-Casanova P, Sarabia Lavín R, González de la Torre H, Verdú-Soriano J. Epidemiology of venous leg ulcers in primary health care: Incidence and prevalence in a health centre-A time series study (2010-2014). *Int Wound J.* 2019 Feb;16(1):256-265.
24. Dutch Society for Dermatology and Venereology. Guideline venous pathology. [In Dutch] 2014. ''https://tinyurl.com/5n8vapfw" [accessed 23 March 2024].
25. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The postthrombotic syndrome: Evidence-based prevention, diagnosis, and treatment strategies: A scientific statement from the American heart association. *Circulation*. 2014 Oct 28;130(18):1636-61.
26. Kahn SR. The post-thrombotic syndrome. *Hematology Am Soc Hematol Educ Program.* 2016 Dec 2;2016(1):413-418.
27. Lurie F, Passman M, Meisner M, Dalsing M, Masuda E, Welch H, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020 May;8(3):342-352.
28. Nicolaides A, Kakkos S, Baekgaard N, Comerota A, de Maeseneer M, Eklof B, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *Int Angiol.* 2018 Jun;37(3):181-254.
29. Santiago FR, Ulloa J, Régnier C, Peudon T, Braund E, Fradet-Aubignat C, et al. The impact of lower limb chronic venous disease on quality of life: patient and physician perspectives. *J Comp Eff Res.* 2022 Aug;11(11):789-803.
30. Lazar M, Ershadi S, Bolton L, Phillips T. Patient-centered Outcomes for Individuals with a Venous Leg Ulcer: A Scoping Review. *Adv Skin Wound Care.* 2023 Jan 1;36(1):10-17.
31. Cleman J, Xia K, Haider M, Nikooie R, Scierka L, Romain G, et al. A state-of-the-art review of quality-of-life assessment in venous disease. *J Vasc Surg Venous Lymphat Disord.* 2024 Jul;12(4):101725.
32. Santiago F. Quality of Life in Chronic Venous Disease: Bridging the Gap Between Patients and Physicians. *Clin Drug Investig.* 2023 Jun;43(Suppl 1):3-8.
33. Rabe E, Pannier F. Societal costs of chronic venous disease in CEAP C4, C5, C6 disease. *Phlebology*. 2010 Oct;25 Suppl 1:64-7.
34. Varatharajan L, Thapar A, Lane T, Munster AB, Davies AH. Pharmacological adjuncts for chronic venous ulcer healing: a systematic review. *Phlebology*. 2016 Jun;31(5):356-65.
35. Michaels JA, Campbell WB, Brazier JE, Macintyre JB, Palfreyman SJ, Ratcliffe J, et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol Assess.* 2006 Apr;10(13):1-196, iii-iv.

36. National Institute for Health and Care Excellence (NICE). Varicose veins: diagnosis and management Clinical guideline [Internet]. 2013. Available from: www.nice.org.uk/guidance/cg168 [accessed 16 May 2024].
37. Epstein D, Bootun R, Diop M, Ortega-Ortega M, Lane TRA, Davies AH. Cost-effectiveness analysis of current varicose veins treatments. *J Vasc Surg Venous Lymphat Disord.* 2022 Mar;10(2):504-513.e7.
38. Rognoni C, Lugli M, Maleti O, Tarricone R. Venous stenting for patients with outflow obstruction and leg ulcers: cost-effectiveness and budget impact analyses. *J Comp Eff Res.* 2020 Jul;9(10):705-720.
39. Epstein DM, Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, et al. Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. *Br J Surg.* 2019 Apr;106(5):555-562
40. Nawasrah J, Zydek B, Lucks J, Renczes J, Haberichter B, Balaban Ü, et al. Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis - results of the Iliaca-PTS - Registry. *Vasa*. 2021 Jan;50(1):30-37.
41. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: A recommendation for standardization. *J Thromb Haemost.* 2009 May;7(5):879-83.
42. Passman MA, McLafferty RB, Lentz MF, Nagre SB, Lafrati MD, Bohannon WT, et al. Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National Venous Screening Program. *J Vasc Surg*. 2011;54(6 SUPPL.).
43. Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. Validation of the Villalta scale in assessing post-thrombotic syndrome using clinical, duplex, and hemodynamic comparators. *J Vasc Surg Venous Lymphat Disord.* 2014 Jan;2(1):8-14.
44. Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. *Haemostasis*. 1994;24:158a
45. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost.* 2009 May;7(5):884-8.
46. Isoherranen K, Kallio M, O`Brien JJ, Lagus H, Clinical characteristics of lower extremity ulcers. *J Eur Wound M Ass.* 2020 Nov 12;21(Issue 1 Volume 21, 2020):51–8.
47. Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. *N Engl J Med.* 2017 Oct 19;377(16):1559-1567.
48. Probst S, Saini C, Gschwind G, Stefanelli A, Bobbink P, Pugliese MT, et al. Prevalence and incidence of venous leg ulcers-A systematic review and meta-analysis. Int Wound J. 2023 Nov;20(9):3906-3921.
49. Schneider C, Stratman S, Kirsner RS. Lower Extremity Ulcers. *Med Clin North Am*. 2021 Jul;105(4):663-679.
50. Rinfret F, Gu CS, Vedantham S, Kahn SR. New and known predictors of the postthrombotic syndrome: A subanalysis of the ATTRACT trial. *Res Pract Thromb Haemost.* 2022 Aug 29;6(6):e12796.
51. Schulman S, Lindmarker P, Holmström M, Lärfars G, Carlsson A, Nicol P, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost.* 2006 Apr;4(4):734-42.
52. Caggiati A, De Maeseneer M, Cavezzi A, Mosti G, Morrison N. Rehabilitation of patients with venous diseases of the lower limbs: State of the art. *Phlebology*. 2018 Dec;33(10):663-671.
53. Fife CE, Eckert KA, Carter MJ. Publicly Reported Wound Healing Rates: The Fantasy and the Reality. *Adv Wound Care (New Rochelle)*. 2018 Mar 1;7(3):77-94.

54. Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. *Phlebology*. 2018 Apr;33(3):163-184.

55. Shi C, Dumville JC, Cullum N, Connaughton E, Norman G. Compression bandages or stockings versus no compression for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2021 Jul 26;7(7):CD013397.

56. Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur J Vasc Endovasc Surg.* 2021 Jan;61(1):9-82.

57. Van Hecke A, Grypdonck M, Defloor T. Interventions to enhance patient compliance with leg ulcer treatment: a review of the literature. *J Clin Nurs.* 2008 Jan;17(1):29-39.

58. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2012 Nov 14;11(11):CD000265

59. Ten Cate-Hoek AJ, Bouman AC, Joore MA, Prins M, Ten Cate H; IDEAL DVT trial investigators. The IDEAL DVT study, individualised duration elastic compression therapy against long-term duration of therapy for the prevention of post-thrombotic syndrome: protocol of a randomised controlled trial. *BMJ Open.* 2014 Sep 4;4(9):e005265.

60. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol.* 2018 Jan;5(1):e25-e33.

61. Amin EE, Joore MA, Ten Cate H, Meijer K, Tick LW, Middeldorp S, et al. Clinical and economic impact of compression in the acute phase of deep vein thrombosis. *J Thromb Haemost.* 2018 Jun 1.

62. Araujo DN, Ribeiro CT, Maciel AC, Bruno SS, Fregonezi GA, Dias FA. Physical exercise for the treatment of non-ulcerated chronic venous insufficiency. *Cochrane Database Syst Rev.* 2016 Dec 3;12(12):CD010637.

63. Deol ZK, Lakhanpal S, Franzon G, Pappas PJ. Effect of obesity on chronic venous insufficiency treatment outcomes. *J Vasc Surg Venous Lymphat Disord.* 2020 Jul;8(4):617-628.e1.

64. Gürdal Karakelle S, Ipek Y, Tulin O, Alpagut İU. The efficiency of exercise training in patients with venous insufficiency: A double blinded, randomized controlled trial. *Phlebology*. 2021 Jul;36(6):440-449

65. McIntosh E, Horspool M, Levesley M, Logan P, Klonizakis M. co-design of an exercise-based, lifestyle intervention for people with venous leg ulcers; a self-care, expert-supported strategy for a chronic condition. *Int Wound J.* 2023 Sep;20(7):2528-2539.

66. Bolton Saghdaoui L, Lampridou S, Racaru S, Davies AH, Wells M. Healthcare interventions to aid patient self-management of lower limb wounds: A systematic scoping review. *Int Wound J.* 2023 Apr;20(4):1304-1315.

67. Jull A, Slark J, Parsons J. Prescribed exercise with compression vs compression alone in treating patients with venous leg ulcers a systematic review and meta-analysis. *JAMA Dermatol*. 2018 Nov 1;154(11):1304-1311.

68. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021 Dec;160(6):e545-e608.

69. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev.* 2014 Jan 10;2014(1):CD003557.

70. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. *Int J Mol Sci.* 2018 Jun 5;19(6):1669.

71. Gianesini S, De Luca L, Feodor T, Taha W, Bozkurt K, Lurie F. Cardiovascular Insights for the Appropriate Management of Chronic Venous Disease: A Narrative Review of Implications for the Use of Venoactive *Drugs. Adv Ther.* 2023 Dec;40(12):5137-5154.

72. Briggs M, Nelson EA, Martyn-St James M. Topical agents or dressings for pain in venous leg ulcers. *Cochrane Database Syst Rev. 2012* Nov 14;11(11):CD001177.

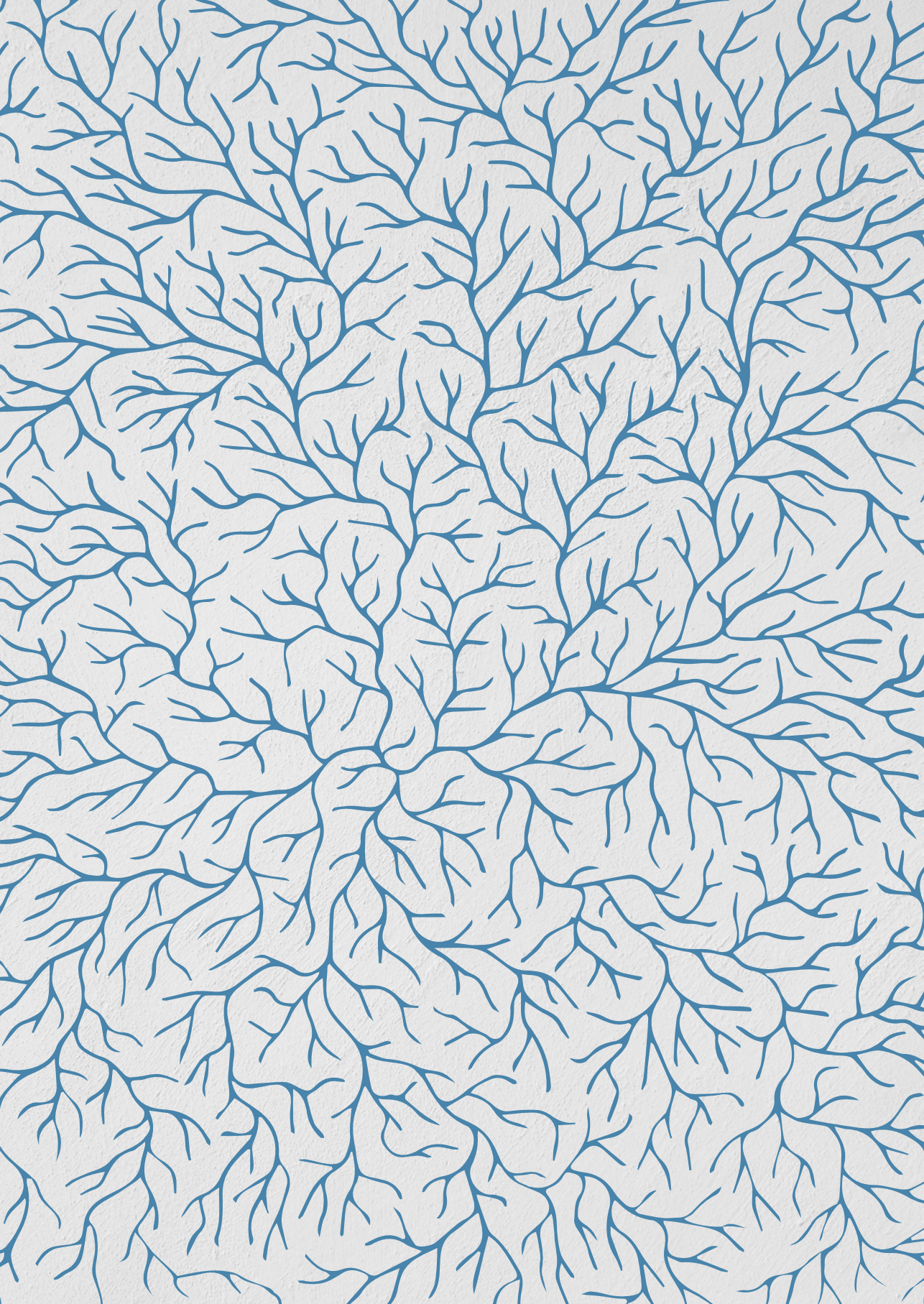
73. Omeara S, Martyn-St James M. Foam dressings for venous leg ulcers. *Cochrane Database Syst Rev.* 2013 May 31;2013(5):CD009907.

74. Norman G, Westby MJ, Rithalia AD, Stubbs N, Soares MO, Dumville JC. Dressings and topical agents for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2018 Jun 15;6(6):CD012583.

75. Gloviczki P, Lawrence PF, Wasan SM, Meissner MH, Almeida J, Brown KR, et al. 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part II: Endorsed by the Society of Interventional Radiology and the Society for Vascular Medicine. *J Vasc Surg Venous Lymphat Disord.* 2024 Jan;12(1):101670.

PART ONE

Comprehensive treatment and follow-up care during and after visit to the one-stop clinic for venous leg ulcers



Chapter 2

Evaluation of the introduction of the one-stop clinic and dedicated nurses for venous leg ulcer care in the East of the Netherlands

Bram Rook
Miriam Wikkerink
Ilse E.B.M. Kroft

A version of this chapter was previously published in: Phlebology. 2020 Feb;35(1):27-38.

ABSTRACT

Objective: In the ZGT hospital nurses from two community care organizations were trained to visit patients at home and provide adequate ulcer care. Furthermore, the one-stop clinic was introduced to set a diagnosis and treatment plan at the first visit in the hospital. The purpose of this study was to (a) evaluate if there is a difference in time to wound healing for patients with VLU treated by dedicated nurses compared to treatment by nurses in the Dermatology outpatient clinic and (b) determine if the one-stop clinic setting would lead to a difference in time to wound healing compared to the standard way of care.

Methods: In this retrospective cohort study, all files of patients with an ulcer in the Dermatology department of ZGT between 1st June 2010 and 1st June 2015 were studied.

Results: Out of a total of 385 new patients with an ulcer, 97 cases were included. Patients who were treated by dedicated nurses were significantly older (p=0.002) and had larger wounds (p=0.008). Age was not significantly related to time for wound closure (HR 0.99; 95% CI: 0.97–1.01, p=0.226). After adjustment for confounders, there was no significant difference in time to wound closure between dedicated nurses (2.2 months (1.4–3.0)) versus hospital care (2.3 months (2.1–2.6)) (HR 1.01; 95% CI: 0.61–1.67, p=0.961). The one-stop clinic led to a statistically shorter time to closure of the wound (1.8 versus 2.7 standard way of care, p=0.007).

Conclusions: Time to wound closure is not statistically different between patients treated by dedicated nurses compared to hospital care when adjusted for the effects of the one-stop clinic. The one-stop clinic gives a significant better chance for faster time to wound closure controlled for both groups.

INTRODUCTION

A venous leg ulcer (VLU) is the most prevalent cause of a leg ulcer. German studies show that the prevalence of general ulcer cruris in the general population is 1% and in individuals above 80 years between 4% and 5%.[1] Women are about three times more at risk of getting an ulcer compared to men.[2] Besides having an older age, there are other risk factors for VLU, these include varicose veins, vein abnormalities, multiple pregnancies, obesity, previous leg injuries (trauma), phlebitis, surgery and deep venous thrombosis (DVT).[3] Leg ulcers can be divided into categories such as venous, arterial and venous-arterial, also known as mixed ulcers.[4] The majority of lower limb ulcers are caused by venous disease. Some ulcers can be caused by trauma, skin malignancies, inflammatory skin diseases (e.g. necrobiosis lipoidica, scratch wounds by eczema), infections (e.g. bullous erysipelas) and other factors. The Lothian and Forth Valley Study showed that among 600 patients with ulcer cruris, 76% were caused by venous disease and 22% by arterial disease.[5] Concerning the mechanism of ulceration, or in other words the process of ulceration, pericapillary fibrin cuff formation, trapping of white blood cells and growth factors have been proposed as possible mechanisms of ulcerations.[6] Venous ulcers can cause various symptoms: pain, itching, heaviness, leg-tiredness, cramps, burning and swelling.[7] Ulcers are debilitating and painful and can greatly reduce patients' quality of life (QOL).[4] Ulcer healing has been shown to restore QOL.[4]

The number of patients with VLU is increasing because of growing life expectancy and while more people develop obesity with its side effects. Moreover, since patients visit a hospital when the wound does not heal after a period of time, it is important to set the correct diagnosis as soon as possible. By setting a correct diagnosis, proper treatment can take place, resulting in a shorter time to wound healing and simultaneously cost reduction is expected.

Most patients with VLU are elderly, which requires significant effort for them to make frequent visits to the hospital. The dermatologists of the ZGT hospital, i.e. Hengelo and Almelo, and the community care organizations Carintreggeland and ZorgAccent came up with a plan to train nurses of community care organizations with Dermatology department nurses who daily practice the wound care at the outpatient clinic of the Dermatology department in the ZGT. A Canadian study from 2011 already showed that the organization of care rather than the location or way of care delivery is more important.[8] This is why we trained the nurses the same method of wound care as in the hospital. This collaboration was implemented by the Dermatology department of the ZGT.

These trained community care nurses (dedicated nurses) visit the ulcer patients at home and give appropriate wound care and if necessary compression therapy. Patients can now be treated at home which makes the need for visits to the hospital no longer necessary. The quality of care is similar between care in a hospital setting and community care by dedicated nurses, but only if the care is well organized.[8,9] Furthermore, at the ZGT, the one-stop clinic was introduced for faster diagnosis and identifying which patients could be treated at home rather than within the hospital setting. In one visit, the medical history, physical examination and additional (vascular) examinations are performed. After this and still during the first visit, the diagnosis and the individual ulcer treatment plan are made. This new method is unique in the Netherlands. Although not much evidence is available about this subject yet, we suspect that patients prefer care within their homes, and that through this approach (including faster diagnosis), wounds would heal faster and therefore makes this approach more cost-efficient.

Objectives

We performed this retrospective study to investigate if there is a difference in time to wound healing for patients with VLU treated by dedicated nurses compared to treatment by nurses in a Dermatology outpatient clinic. Another aim of this study was to assess if the one-stop clinic (faster diagnosis) leads to a faster time to wound closure.

Diagnosis of ulcer cruris in the ZGT

Besides the medical history and physical examination, additional examination will be performed. The tests which are used for the evaluation of the vascular functions are the ankle-brachial pressure index (ABPI), duplex ultrasound and on indication toe brachial index (TBI).

Diagnosis for superficial venous reflux is available because of the duplex ultrasound scanning, which is the golden standard for accurate evaluation of the highest point of valve failure and extent of reflux.[10,11] That is the best way to confirm or exclude the presence of venous dysfunction. Duplex can determine whether the deep veins or the greater or lesser saphenous veins and their tributaries are dilated, congested or incompetent. It can also detect the presence of incompetent perforating veins and if the problem is caused by anatomical obstruction, reflux or both.[12] Venous incompetence was identified by reverse flow lasting >0.5 seconds following the release of firm calf compression.[13] In the ZGT, the most common tools for diagnosing ulcers are medical history, physical examination and vascular examination such as Duplex scanning, ABPI and TBI. Laboratory tests are sometimes performed as well,

which could include blood testing or cultures. The ABPI is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery.[14] However, the ABPI may not always be reliable, particularly in patients with diabetes where vascular calcification can prevent arterial compression and falsely increase arterial systolic pressure and therefore the ABPI.[15] The ABPI may thus be confounded in diabetic patients, because of calcification of the arteries. In that case, the TBI can be performed.[15]

After gathering all this information, the dermatologist makes a diagnosis/differential diagnosis. Sometimes additional tests are needed, for instance skin biopsy, blood samples and culture samples.

Methods of treatment for venous leg ulcers

Treatment of patients with VLU is either conservative (compression therapy) or/and also with venous intervention. In general, the treatment goals are to reduce edema, improve ulcer healing and prevent recurrence.[12] With appropriate treatment, most of these ulcers will heal within 3 to 4 months.[16]

Compression therapy

Compression therapy aims to increase venous and lymphatic return, reducing oedema and venous pressure in the limb, by the application of an external force. Compression therapy is the standard care for venous ulcers.[17] Compression treatment increases the healing of ulcers compared with no compression. More ulcers were healed with high compression systems than with low compression systems, but should only be used in the absence of significant arterial disease.[18] No clear differences in the effectiveness of different types of compression systems (multilayer and short stretch bandages) have been shown. A meta-analysis showed that adequate compression therapy is not only important for the healing of venous insufficiency and ulcers but that continuing the compression after the ulcer has healed is also critical for the recurrence-free interval.[19] In addition to compression therapy, education is also important for both the healing process and to prevent recurrence, i.e. to inform the patient about the ulcer, the healing time and the importance of the treatments.[20] In addition to the VLU protocol, the patient is advised about their lifestyle: prevent immobility, stimulate to use the muscle calf pump, prevent obesity and discourage smoking.[21]

(Venous) treatments

Different techniques are available in the ZGT, including 'foam'-sclerotherapy, endovenous radiofrequent ablation for the incompetent veins and ambulant phlebectomy according to Muller.[22]

Wound care and wound care materials

No level 1 evidence is available that any wound dressing confers specific benefit over another.[12] In the ZGT, alginate dressings, hydrofibres, hydrocolloids, hydrogels, wound edge protectors, foam and silver, paraffin and silicon dressings were used.

Ulcer care ZGT

The care path of patients with VLU before implementation of the dedicated nurses and the one-stop clinic is illustrated in figure 1. This method led to delay while the appointments and additional tests took place on different days during the process, often within one week.

Until the year 2014, ZGT Almelo was using this 'old method,' and until the year 2004, ZGT Hengelo was using this 'old method'. The old method is the procedure in which venous ulcer care in the Netherlands in most Dermatology departments is structured and therefore representative for the standard care of venous ulcer care. Patients with VLU first went to the general practitioner (GP). If the wound did not heal, or when the GP had doubt about the diagnosis, the patient was referred to the hospital. After multiple outpatient visits, the diagnosis can be made (figure 1). After the diagnosis, a treatment plan was prepared by the dermatologist. After this, the patient has to visit the hospital each time for the treatment and care of the ulcer wound by the dermatologist (nurse).

ZGT introduction of the one-stop clinic and the dedicated nurses

The new method might be more time-saving by doing the different kinds of examinations and making the treatment plan during the first consult in the hospital. This is expected to save time because of fewer necessary consultations and thereby also less waiting time compared with the old method.

One-stop clinic

Since 1997, the Dermatology outpatient clinic of ZGT cooperates with nurses who are dedicated in taking care of ulcer patients. Since the year 2014 during the first consultation at the hospital, every ulcer patient receives a medical history, physical examination, additional examination, i.e. duplex ultrasound and ABPI and on indication TBI, laboratory tests and/or biopsy. After performing this, the diagnosis

and the individual ulcer treatment plan are made. Information about the patient is (after informed consent is secured) exchanged with the dedicated nurses. Then information about the ulcer is given to the patient and a letter about the current state of the patient, the ulcer and the treatment plan is sent to the GP. In figure 2 the one-stop clinic is illustrated in more detail.

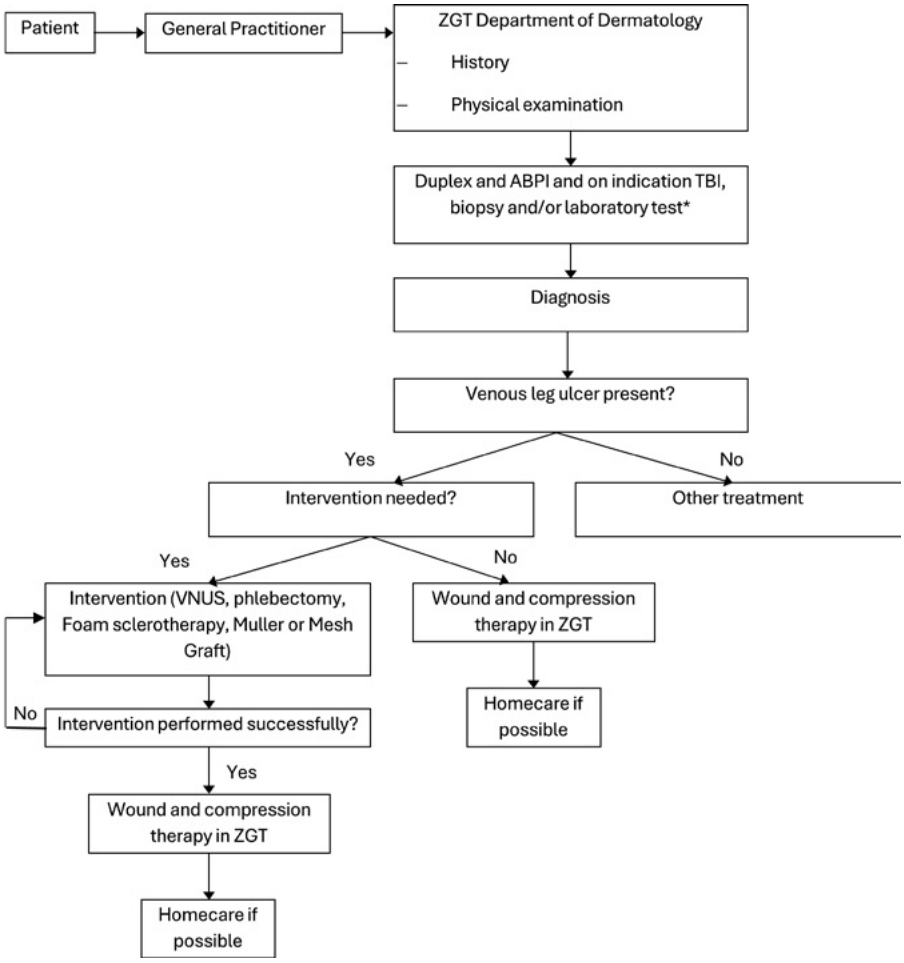


Figure 1. Overview of the old method. More visits were needed before a diagnosis was made. The patient receives care in the hospital. *ABPI: ankle-brachial pressure index; TBI: toe brachial index; VNUS: endovenous radiofrequent ablation*

*Additional tests took place on another day and patients had to come back for the results.

If the diagnosis during the first consult in the hospital shows that the ulcer is of venous origin, then two options of treatment are possible:

1. Conservative treatment (figure 2): No treatment is possible, for example the patient has deep venous insufficiency. In this case, only the intake (medical history and physical examination) and vascular examination are performed by the dermatologist. Immediately after that, the patient is referred back to the GP and the dedicated nurses are activated. The GP becomes main therapist again.

2. Venous treatment (figure 2): In case of superficial venous insufficiency, the patient still remains under the supervision of the dermatologist and is also controlled by the dermatologist. This remains so until venous intervention of the underlying cause has been performed by the dermatologist. Then the patient will be referred back to the GP. The GP becomes the main therapist again and the dedicated team is activated. If the state of the VLU becomes worse, for example larger, then the dedicated nurse can directly contact the dermatologist.

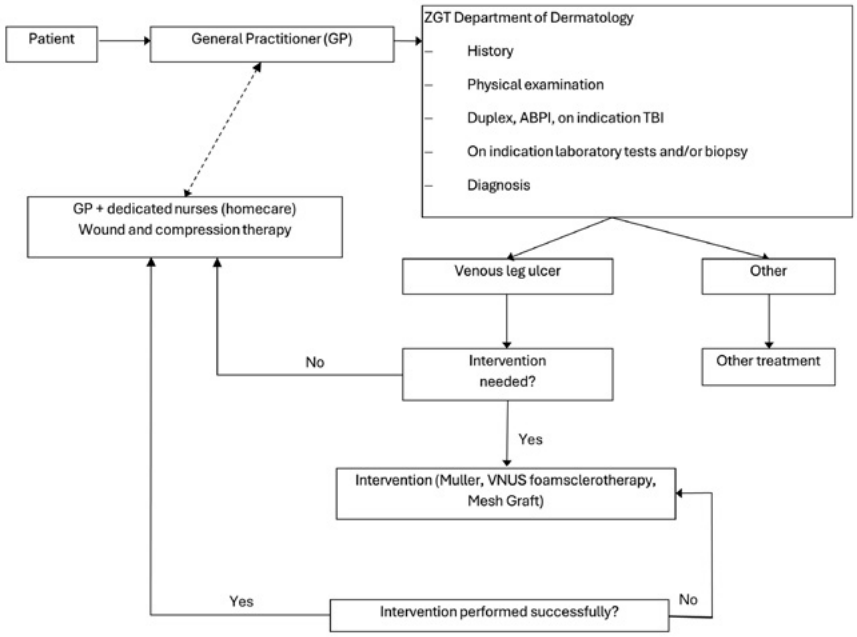


Figure 2. Overview of the one-stop clinic. During the "First consult" the anamneses, physical examination, vascular research and the diagnosis are performed in one day. Sometimes when laboratory test and/or biopsy is taken, the diagnosis comes later.

ABPI: ankle-brachial pressure index; TBI: toe brachial index; VNUS: endovenous radiofrequent ablation

The nurse team with a dedicated nurse

Specific education and qualification requirements are required for a nurse to become a dedicated nurse. The education requirements are:

- To become a certified dedicated wound nurse, a nurse must follow a training that consists of eight sessions with an experienced dedicated nurse and two sessions at the ZGT with a dermatology nurse of the ZGT and with the dermatologist.
- Also the nurse must receive three sessions of theoretical training: two sessions (accredited by the dedicated nurse) and one session phlebological education by a dermatologist.
- The team of nurses is trained twice a year by a dedicated nurse (for ulcers) from Carintreggeland and once a year at an education course by a dermatologist of ZGT.
- The team has to participate two times a year in patient discussions.
- The education level of a nurse (for treating ulcers) must at least be level four of the secondary vocational education.
- The dedicated nurses must spend at least 10 hours a week on ulcer treatment and/or compression therapy.

The dedicated nurse in practice

Dedicated nurses are especially trained to treat ulcer patients with wound care and compression therapy. Because of these dedicated nurses, the ulcer patients do not have to go to the hospital to be taken care of, but instead these dedicated ulcer nurses go to the patients' home. Usually a dedicated nurse visits the patients at home twice a week, but if necessary more often. The dedicated ulcer nurses have close communication with the dermatologist and nurses in the ZGT and with the GP. The nurses of ZGT, dedicated nurses of Carintreggeland and ZorgAccent cooperate together and use the same type of wound material to bind and clean the wound. So when in a case a nurse from Carintreggeland has to take over from a nurse from ZorgAccent or vice versa, then this can be done without problems. Also currently there is more economical use of wound materials. As an example, previously leg bandages would be used once and then they would be thrown away. Nowadays wound bandages can be washed and reused again for two or three times. Furthermore, the nurses also work according to the same guidelines, such as the way to bind wounds and which wound products to use. They also report their data according to standardized dossier compilation.

Summary of the advantage of one-stop clinic and the dedicated nurses

In summary, the advantage of the one-stop clinic and the dedicated nurses team in comparison to the old method of care is that the total care path from the beginning till the end takes less time, there is better communication between the nurses, there are special working guidelines and standardized medical records compilation for reporting data and there is more economical use of wound care products.

Research questions

- The following are the aims of this study: Is the time to wound healing for patients with VLU faster with the deployment of dermatologist nurses in the hospital compared to treatment by dedicated nurses?
- Does the one-stop clinic (faster diagnosis) lead to a faster time to wound closure?

METHODS

Study design

This research study is a retrospective cohort study.

Setting

All the files of patients in the Dermatology department of ZGT in Almelo and Hengelo between June 1st 2010 and June 1st 2015 examined with a leg ulcer were studied. All cases were evaluated by one physician. After this, 385 patients were selected (figure 3).

Participants

Patients were included when they had VLU and were 18 years or older. All ulcer sizes were included. Of patients with a VLU on both legs, the largest ulcer was included for analysis.

Exclusion criteria were patients with other causes of leg ulcer, e.g. arterial leg ulcers, ulcer of Martorell, livedo vasculopathy, mixed ulcer: ulcer has both arterial and venous cause. Furthermore, patients with an ankle pressure <60 mmHg and other causes of ulcers that did not have only a venous cause were excluded. Also patients under the age of 18 years old and also mentally disabled patients (as dementia) were not included in the research study. Patients with multiple episodes of VLU were excluded. Other exclusion criteria were patients treated by family/GP or other community care organizations after visiting the ZGT.

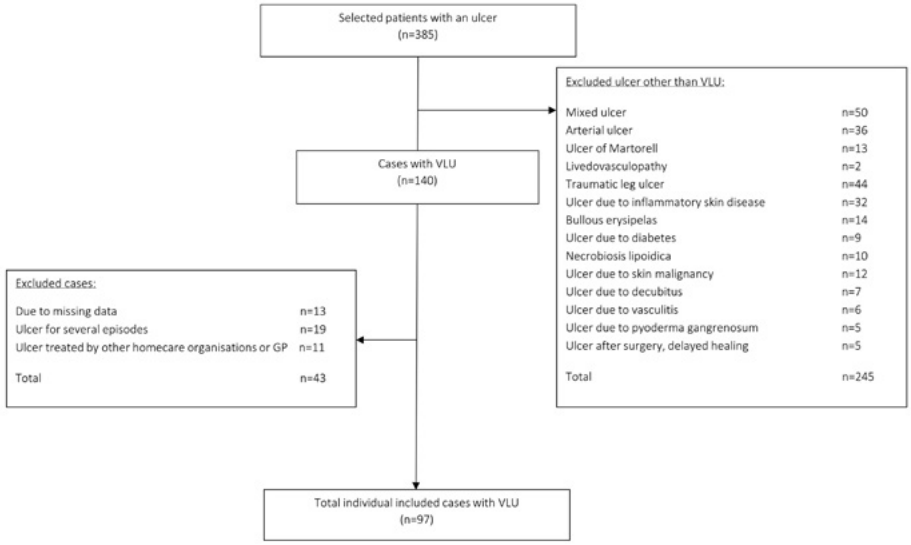


Figure 3. Flowchart of patient selection
VLU: venous leg ulcer; GP: General Practitioner.

Study variables

All files were searched and the following variables were identified: patient number, sex, date of birth, date of first visit, age at first visit, number of visits to the hospital, number of visits to a certain caretaker, ulcer side, ulcer size, type of ZGT method, type of treatment, state of closure of the wound, date of wound closure, first and last date of community care, number of treatments by community care and number of dedicated nurses at home. No differentiation was made between post thrombotic and superficial venous insufficiency.

Patient groups

The patients were assigned to groups based on clinical decision. The following are the group of patients belonging to different kind of 'care methods':

1. Patients who were treated via the one-stop clinic and treated with the dedicated nurses (one-stop+DDN) (New method)
2. Patients who were treated oat the one-stop clinic and were treated only in the ZGT; therefore, no participation of the dedicated nurses (one-stop+ZGT) (Transitional phase old and new method)
3. Patients who were not treated at the one-stop clinic, but by the dedicated nurses (no one-stop+DDN) (Transitional phase old and new method)

4. Patients who were not treated at the one-stop clinic and were treated only in the ZGT (no one-stop+ZGT) (Old method)

To compare dedicated nurses to ulcer care in the hospital, we combined groups 1 and 3 and groups 2 and 4 due to small group sizes. Due to small group sizes, we combined groups 1 and 3, named DDN and groups 2 and 4, named ZGT.

Primary outcome variables

- The first primary outcome variable is time to wound healing for patients with VLU treated by dedicated nurses compared to treatment by nurses in a hospital setting.
- The second primary outcome is the time to wound closure in patients treated via the one-stop clinic compared to treatment without the one-stop clinic pathway.

Statistical methods

Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR); categorical variables as counts with corresponding percentages. Difference in baseline characteristics between groups was tested using independent t-test or Mann-Whitney U test (continuous variables) or chi-square (categorical). We analysed time to wound healing by Kaplan-Meier survival curves. We used univariate and multivariate Cox proportional hazard regression models to establish the relationship of treatment (ZGT vs. DDN and one-stop clinic vs. no one-stop clinic) with time to wound healing. Baseline characteristics that showed significant differences between groups were further analysed using univariate Cox proportional hazard regression to explore potential confounding effects on the relation between treatment group and time to wound healing. A p value of 0.150 or lower was included in the multivariate Cox regression model.

RESULTS

Patient characteristics

Of the total 345 cases, 97 cases were included for analysis: group 1: n = 26 (male 12), group 2: n = 16 (male 8), group 3: n = 23 (male 8) and group 4: n = 32 (male 15). To compare dedicated nurses to ulcer care in the hospital, we combined groups 1 and 3, named DDN, and groups 2 and 4, named ZGT, due to small group sizes. From here, we will use DDN group and ZGT group.

Of these 97 cases (male n = 43, female n = 45) with a median age of 70.6 years (interquartile range 23.7, minimum 30.4, maximum 93.6 years), the median ulcer size was 2.0 cm^2 (interquartile range 3.5 cm^2, minimum 0.01 cm^2-165.0 cm^2) and the median time to wound closure was 2.4 months (95% CI 1.9–2.9 months).

Baseline characteristics of all initial groups are shown in table 1. We combined the groups and compared them using descriptive statistics. These results are shown in table 2. Patients treated by dedicated nurses were significantly older (p=0.002) and had larger wounds (p=0.008) compared to the ZGT group.

Table 1. Baseline characteristics of the initial groups.

Variable	One-stop+DDN	One-stop+ZGT	No one-stop+DDN	No one-stop+ZGT
Total patients, *n* (%)	26 (100)	16 (100)	23 (100)	32 (100)
Sex (M/F), *n* (%)	14 (54)/12 (46)	8 (50)/8 (50)	15 (65)/8 (35)	17 (53)/15 (47)
Median age at first visit, *years* (IQR)	73.4 (20.0)	62.8 (27.6)	79.9 (15.5)	66.3 (28.2)
Median ulcer size*, *cm2* (IQR)	3 (9.1)	0.5 (3.3)	2 (8.0)	1 (2.5)
Median number of visits, *n* (IQR)	3.0 (4.0)	5.5 (7.0)	4.0 (5.0)	6.0 (3.0)
Total patients one-stop clinic, *n (%)*	26 (100)	16 (100)	0 (0)	0 (0)
Total patients DDN, *n* (%)	16 (100)	0 (0)	23 (100)	0 (0)
Median time to wound closure, *n* (95% CI)	2.7 (1.6-2.6)	1.8 (1.1-2.5)	2.7 (0.0-5.9)	2.7 (2.2-3.2)

Male; F: female; IQR: Interquartile range; DDN: Dedicated dermatology nurse; ZGT: Ziekenhuisgroep Twente; 95 CI: 95% Confidence interval. *The size of the wound was not known in all patients.

Table 2. Descriptive data of the combined groups (1+3 and 2+4).

Variable	DDN	ZGT	p-value
Total patients, *n* (%)	49 (100)	48 (100)	
Sex (M/F), *n(%)*	20 (41)/29 (59)	23 (48)/25 (52)	0.482
Median age at first visit, *years* (IQR)	75.6 (16.8)	65.5 (24.5)	**0.002**
Median ulcer size*, *cm*^{2} (IQR)	2.6 (8.0)	1.0 (2.5)	**0.008**
Median number of visits, *n* (IQR)	4.2 (4.0)	6.4 (5.0)	**0.002**
Total patients one-stop clinic, *n* (%)	26 (53)	16 (33)	0.050

M: male; F: female; IQR: Interquartile range; DDN: Dedicated dermatology nurse; ZGT: Ziekenhuisgroep Twente. P-values that are significant (P<0.05) are reported bold.
*The size of the wound was not known in all patients: DDN n=40, ZGT n=37

Primary results

The median time to wound closure in the Kaplan– Meier analysis was 2.2 (95% CI 1.4–3.0) months in the DDN group and 2.3 (95% CI 2.1–2.7) months in the ZGT group (p=0.620). This was not a statistical difference. Survival analysis is shown in figure 4.

Treatment via the one-stop clinic led to a statistically shorter time to wound closure. No one-stop clinic had a median time to wound closure of 2.7 (95% CI 2.1–3.3) months versus a median time to wound healing of 1.8 (95% CI 1.4–2.6) months in the one-stop clinic (p=0.007). After Cox regression analysis, this led to a greater chance of wound closure in patients treated via the one-stop clinic (HR 2.0; 95% CI 1.2–3.3, p=0.008).

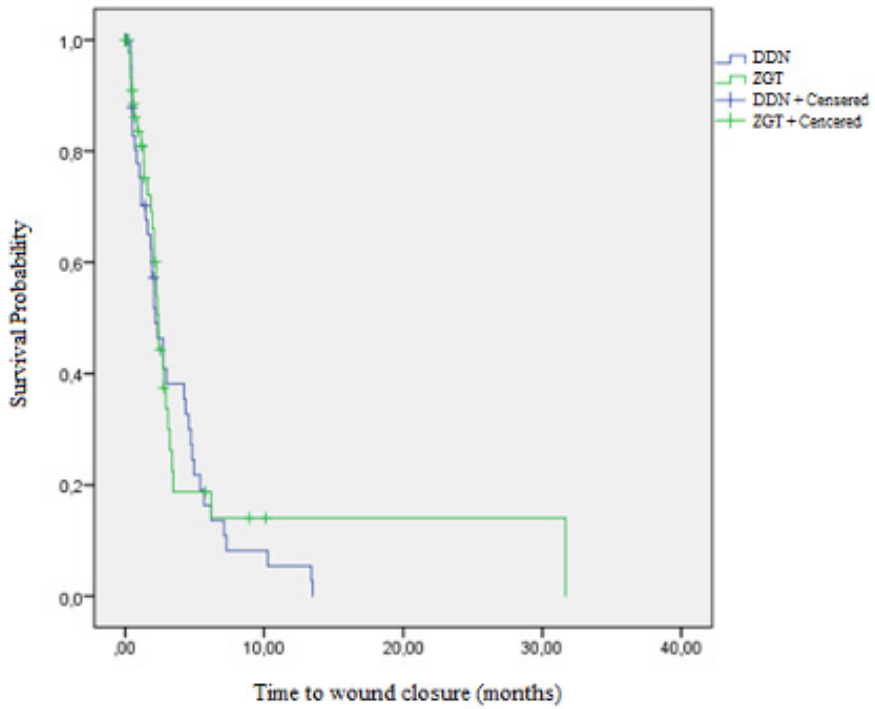


Figure 4. Kaplan-Meier curve of survival in patients with VLU till wound closure. DDN consists of initial group 1 and 3 a ZGT consists of the initial group 2 and 4. *DDN: Dedicated dermatology nurse; ZGT: Ziekenhuisgroep*

Secondary results

The median time to wound closure was 2.3 months, when no venous intervention occurred, with venous intervention, also 2.3 months. The median time for wound

healing was not statistically different between patients who had a venous intervention (p=0.621) and patients without any of these interventional treatments. There was no significant difference between both groups (DDN vs. ZGT) in the number of venous/ mesh graft treatments (p=0.476).We did not observe any confounding effect of the number of invasive treatment influencing the time of healing (p=0.545). Regardless of number of treatment there was no confounding effect of invasive treatment on the time to wound closure (p=0.356). Neither was age at first visit a confounder of time to wound healing (p=0.358).

After adjustment for confounding factors at the one-stop clinic and ulcer size we did not find significant difference in chance of wound closure between dedicated nurses versus hospital care (HR 1.07; 95% CI: 0.6-2.0, p=0.841) in the multivariate regression analysis. The one-stop clinic was significantly related to greater chance of wound closure (HR 2.36; 95% CI: 1.3–4.3, p=0.005). Size of ulcer was not related to increased chance of wound closure (HR 1.0; 95% CI: 0.9–1.0, p=0.255). Results are listed in table 3.

The purpose of this first retrospective study was to investigate if there is difference in effectiveness in terms of timesaving: time to wound healing for patients with VLU treated by dedicated nurses compared to treatment by nurses in a hospital setting. The answer to this question is that there was no difference in time to wound healing between these two groups; i.e. time to wound closure was not statistically different between patients treated by dedicated nurse compared to hospital care when adjusted for confounders.

The patients who were treated by dedicated nurses were significantly older and had larger wounds. This last finding is interesting, while Margolis et al.[23] reported already that ulcers of ≤6 month's duration and ≤5 cm^2 in area that are treated with compression are highly likely to heal within 24 weeks. Conversely, ulcers of >6 months' duration and >5 cm^2 in area are unlikely to heal within 24 weeks. Overall, these patients were often not treated with venous intervention, due to comorbidity. Age at first visit and the size of the wounds did not confound results to wound closure time. In conclusion, there was no significant difference in the time to wound healing between those treated by the dedicated nurses and the experienced nurses in a hospital setting.

Table 3. Multivariate regression analysis for time to wound closure.

Variable	HR	95.0% CI	p-value
Treatment by DDN	1.07	0.6-2.0	0.841
Age at first visit	1.00	1.0-1.0	0.812
Ulcer size	1.00	0.9-1.0	0.255
Treatment via one-stop clinic	2.36	1.3-4.3	**0.005**

DDN: Dedicated dermatology nurse; HR: Hazard ratio; CI: Confidence interval. P-values that are significant (P<0.05) are reported bold.

The second purpose of this study was to examine if the one-stop clinic leads to faster time to wound closure. In this retrospective study, we found that the one-stop clinic gives a significant shorter time to wound closure. This might be explained by the fact that while during the first visit to this one-stop clinic, duplex and arterial investigations were performed; sometimes, additional laboratory testing and a biopsy were needed. In the past, the additional tests were not always performed or these tests were performed when the ulcer did not heal in a short period of time. Because of this, there was some delay in the proper wound treatment. Nowadays, the correct diagnosis can mostly be stated during first visit, so the correct treatment is given directly. The median time to wound healing was not statistically different between patients who had a venous intervention or mesh graft and patients without any of these treatments.

DISCUSSION

Key results

The first outcome of this study is the effectivity in terms of timesaving: Is the time to wound healing for patients with VLU treated by dedicated nurses shorter, longer or equal compared to treatment by nurses in a hospital setting? This study showed that the time to wound closure is not statistically different between patients treated by dedicated nurses compared to hospital care when adjusted for the effects of the one-stop clinic. This finding is interesting. Most patients were old, for whom we assume it could be difficult to go to a hospital. Care inside their own homes gives more relief for the patients. Since there was no difference in time to wound closure, this suggests that the care can safely be arranged by dedicated nurses, which could be a benefit for these patients. We did observe a significant increased risk in faster time to wound healing in patients treated via the one-stop clinic, controlled for size of wound ulcer and group (dedicated nurse home treatment vs. in-hospital treatment).

Strengths

Between June 1st 2010 and June 1st 2015, 385 patients with a new ulcer were seen in the hospital. Only 140 out of 385 patients had a VLU. The reason of this would be the strict inclusion criteria that were applied. Only patients with a single venous leg ulcer were included, and any underlying comorbidity as arterial dysfunction or diabetic mellitus was excluded.

Limitations

A major limitation is the study design. Retrospective studies may need very large sample sizes for rare outcomes.[24] This makes it difficult to make accurate comparisons between research groups and researchers cannot control exposure or outcome assessment, and instead must rely on others for accurate record keeping. Also in this retrospective study, e.g. retrospective chart review, several known variables for ulcer healing were not taken into account.[25,26] We did not perform research about the socio-economic differences in the groups. We did not know the chronicity of the wound before patients presented at the clinic.[23] This is a major predictive factor in ulcer healing and so a limitation of our study. Also in fifteen cases, patients had multiple episodes of an ulcer, and these cases were excluded; however, we did not take into account the effect of this history of ulcer in the time to wound closure. This could have influenced the total time of healing in the investigated patients.

Because of the diverse pathways of care patients were classified to, four different patient groups were formed. This has led to the small sample sizes, making it difficult to compare groups and interpreting outcomes. Since the old method was not used at the moment of inclusion, these groups would not expand. Therefore, we chose to combine groups.

The whole cohort consisted of patients with a proven venous aetiology of the ulcer. Therefore we can not apply the outcome of the one-stop clinic to every patient with an ulcer, as every patient with an ulcer is nowadays seen via the one-stop clinic. In our cohort patients with multiple or reoccur ulcers were also excluded. Since ulcers have a great tendency to reoccur, this group is not an optimal reflection of the realistic population. These selection bias should been taken into account before generalizing the outcomes to all ulcer patients.

Our second primary outcome was time to ulcer healing in the one-stop clinic versus no one-stop clinic. This applies only for patients with proven venous insufficiency as a consequence of the ulcer. Therefore, we cannot apply the outcome of the one-

stop clinic to every patient with an ulcer, as every patient with an ulcer is nowadays seen via the one-stop clinic. This selection bias has been taken into account before generalizing the outcomes to all ulcer patients.

Analysing the size of the wound was done by estimating the wounds on sight of previously taken pictures since in many cases a tape-measure was not used. Since the wound size was only measured two dimensionally, consequently the depth of the wound was not taken into account. However, since all wounds were assessed by the same physician, interobserver variability was minimized.

Besides the time to wound healing, we planned to identify the cost-effectiveness in patients treated in the setting of hospital care, community care organizations and dedicated nurses. Information such as number of visits, the amount of wound dressings that were used, the number of times gauze was switched and the time (dedicated) nurses spent at the patients home would all be gathered. However, while the information systems of the community care organization were not yet equipped to collect such data, the information was not documented correctly in the records and was therefore limited. Consequently, in this retrospective study, we could not analyse these data accurately. In our daily practice, we find that dedicated nurses, through their extensive knowledge, are much more cost-effective on materials such as gauze, bandages and wound dressings. Identification of the costs of ulcers treated by dedicated nurses compared to the old method would allow health care workers and organizations to be more cost-efficient in the ulcer care. The total cost of ulcer care should be targeted for further research in an extensive multi-centre trial. This way a reduction of costs in ulcer care could be achieved.

We assume that people are more satisfied while receiving treatment at home. However, patient satisfaction has not been addressed in this study and future studies should examine the impact of preference of patients of the way of care on outcome. Furthermore, due to cost-efficiency in the health care nowadays, patients would see a lot of different nurses treating their wounds. In most cases where dedicated nurses were the main therapist, they would be the only one treating each patient. This could increase the patient satisfaction. We therefore suggest further research that includes patient satisfaction, preference of treatment and QOL.

Interpretation

This kind of study had not been previously performed. To our knowledge this is the first study that shows that a one-stop clinic for ulcer cruris patients is very valuable. First, the one-stop clinic gives a significant better chance for faster time to

wound closure for patients with a solitary venous ulcer, because a proper diagnosis is made and a correct treatment can be started directly. We expect this will result in lower costs for these ulcer treatments. Secondly by means of dedicated nurses, the treatment can be arranged at home as good as in the hospital, which must be a benefit for the mostly older patients. However, we suggest further research in a trial with a larger cohort with an intention to treat method since this would better reflect the realistic pathways and treatments of all ulcer patients.

Conclusion

The number of patients with a venous leg ulcer (VLU) is increasing and this mostly affects older people. The disease is often chronic and it has a large impact on the QOL of patients. The wound healing process is a popular topic which has been studied extensively. In the ZGT hospital, we have set up a new way of treating VLU. Nurses of the Dermatology department of the hospital who daily practice wound care trained a limited number of nurses from two community care organizations. These trained dedicated nurses then supplied proper ulcer care at home. Furthermore, the one-stop clinic was introduced at the outpatient clinic of the Dermatology department. In one visit, the medical history, physical examination, additional (vascular) examinations are performed. After this and still during the first visit, the diagnosis and the individual ulcer treatment plan are made. This new method is unique in the Netherlands. The purpose of our study was to evaluate if there is a difference in time for wound healing for patients with VLU treated by dedicated nurses compared to treatment by nurses in the Dermatology outpatient Clinic. Another purpose of this study is to assess if the one-stop clinic (faster diagnosis and treatment) leads to a faster time to wound closure. After studying the files of 385 patients with an ulcer for wound size, number of visits, date at first visit, date of wound closure, which method was used (one-stop or other), and ulcer care in the hospital or by dedicated nurses, 97 patients were included. Patients who were treated by dedicated nurses were significant older and had larger wounds. Age was not significantly related to time to wound closure. This study showed that the time to wound closure is not statistically different between patients treated by dedicated nurses compared to hospital care when adjusted for the effects of the one-stop clinic. The one-stop clinic gives a significant better chance for faster time to wound closure controlled for both groups, because a proper diagnosis is made and a correct treatment can be started directly. This will result in lower costs for these ulcer treatments. Second, by means of dedicated nurses, the treatment can be arranged at home as good as in the hospital, which could be a benefit for many patients.

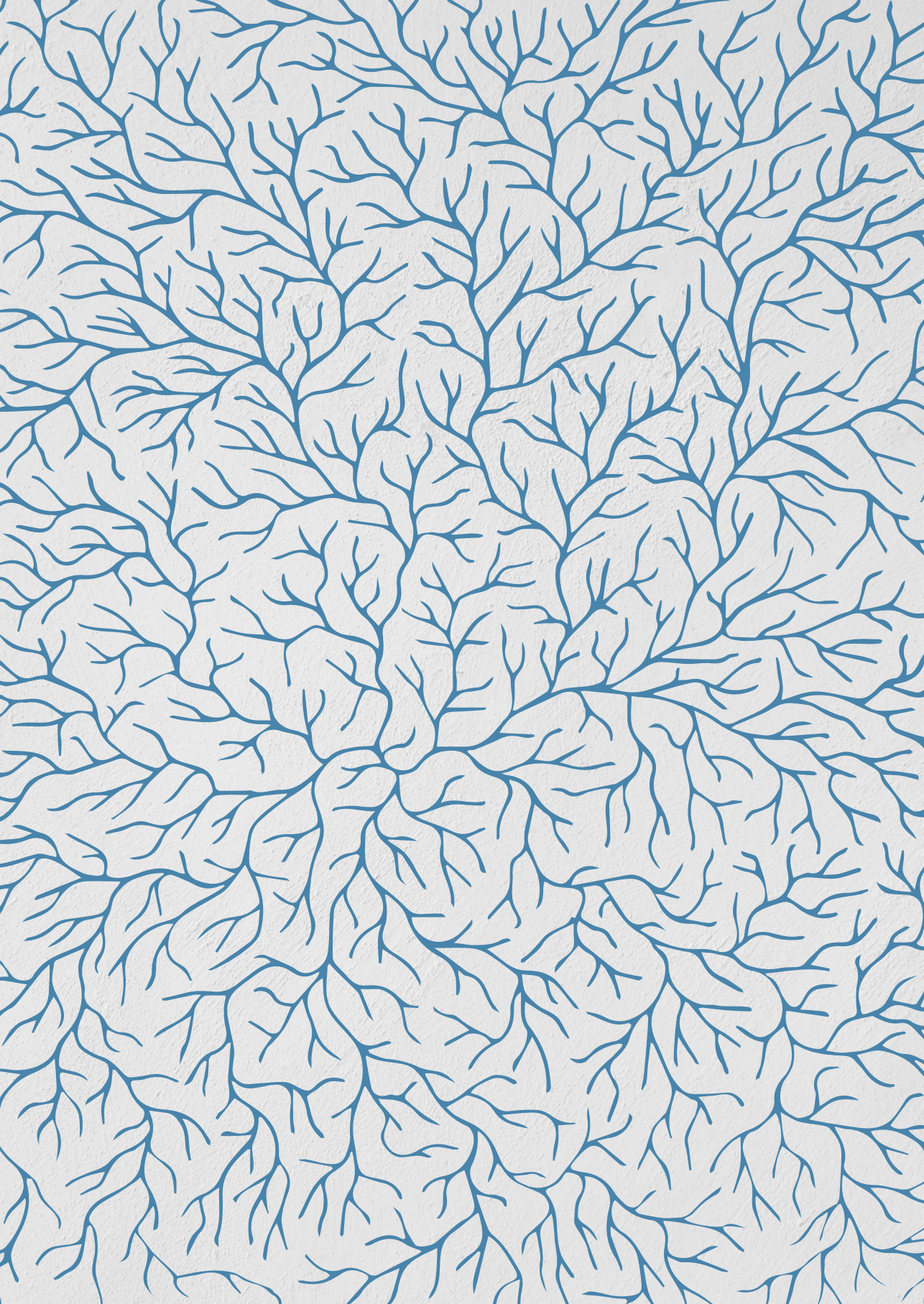
Acknowledgements

The authors want to thank J Timmerman and M Vermeer, PhD (both epidemiologists of the ZGT), R Wijnsma (medical assistant Dermatology ZGT), M Huis in't Veld and A Broekmaat (nurses Dermatology ZGT) and M Beekman (dedicated nurse ZorgAccent) for their help in collecting and analysing the data of the files.

REFERENCES

1. Wissing U and Unosson M. The relation between nutritional status and physical activity, ulcer history and ulcer-related problems in patients with leg and foot ulcers. *Scand J Caring Sci* 1999; 13: 123–128.
2. Callam M, Ruckley C, Harper D, et al. Chronic ulceration of the leg: extent of the problem and provision of care. *BMJ. (Clin Res Ed).* 1985; 290: 1855–1856.
3. Agale S. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. *Ulcers* 2013;2013: article ID 413604, 9 pages.
4. London N and Donnelly R. ABC of arterial and venous disease: ulcerated lower limb. *BMJ.* 2000; 320: 1589–1591.
5. Callam M, Harper D, Dale JJ, et al. Chronic ulcer of the leg: clinical history. *BMJ.* 1987; 294: 1389–1391.
6. Falanga V and Eaglstein WH. The "trap" hypothesis of venous ulceration. *The Lancet.* 1993; 341: 1006–1007.
7. Khachemoune A and Kauffman C. Diagnosis of leg ulcers. *Internet J Dermatol* 2001; 1: 1–8.
8. Harrison MB, VanDenKerkhof E, Hopman WM, et al. Evidence-informed leg ulcer care: a cohort study comparing outcomes of individuals choosing nurse-led clinic or home care. *Ostomy Wound Manage* 2011; 57: 38–45.
9. Harrison MB, Graham ID, Lorimer K, et al. Nurse clinic versus home delivery of evidence-based community leg ulcer care: a randomized health services trial. *BMC Health Serv Res* 2008; 8: 243
10. (NVDV) NVvDeV. Diagnostiek en behandeling van het ulcus cruris venosum. Utrecht: Het Kwaliteitsinstituut voor de Gezondheidszorg CBO, 2005.
11. Whiddon L. The treatment of venous ulcers of the lower extremities. *Proc (Bayl Univ Med Cent)* 2007; 20: 363–366.
12. Van Gent BW, Wilschut E and Wittens C. Management of venous ulcer disease. *BMJ.* 2010; 341: 1092–1096.
13. Dix FP, Picton A, McCollum CN. Effect of superficial venous surgery on venous function in chronic venous insufficiency. *Ann Vasc Surg*. 2005; 19: 678–685.
14. Aboyans V, Criquie M, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation*. 2012; 126: 2890–2909.
15. Spangeus A, Wijkman M, Lindstrom T, et al. Toe brachial Index in middle aged patients with diabetes mellitus type 2: not just a peripheral issue. Diabetes Res *Clin Pract.* 2013; 100: 195–202.
16. Venous leg ulcer. NHS. [Online]. Available from: http://www.nhs.uk/Conditions/Leg-ulcer-venous/Pages/ Introduction.aspx (2014, accessed 8 November 2015).
17. Fletcher A, Cullum N and Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ.* 1997; 315: 576–580.
18. O'Meara S, Cullum N, Nelson EA, Dumville J.C. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2012; 11: CD000265.
19. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. *Cochrane Database of Systematic Reviews.* 2007; 1: CD001836
20. NHG. NHG-Standaard Ulcus cruris venosum, https:// www.nhg.org/standaarden/volledig/nhg-standaard-ulcus-cruris-venosum and https://www.nhg.org/standaarden/ volledig/nhg-standaard-ulcus-cruris-venosum (2015, accessed 28 June 2015).

21. Maessen-Visch M. Maessen-Visch M. Richtlijnen Veneuze pathologie 2014. Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV) 2014; 166–265
22. Ramelet AA. Müller phlebectomy. A new phlebectomy hook. *J Dermatol Surg Oncol.* 1991; 17: 814–816.
23. Margolis DJ, Berlin JA and Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med.* 2000; 109: 15–19.
24. James JN. Retrospective cohort study: strengths and weaknesses. *Tufts Open Courseware.* MA, USA: Tufts University, 2017.
25. Barwell JR, Ghauri ASK, Taylor M, et al. Risk factors for the healing and recurrence of chronic venous leg ulcers. *Eur J Vasc Endovasc Surg.* 2005; 29: 74–77
26. Parker CN, Finlayson KJ, Shuter P, et al. Risk factors for delayed healing in venous leg ulcers: a review of the literature. *Int J Clin Pract*. 2015; 69: 967–977.



Chapter 3

Quality of life of patients with venous leg ulcer treated by a one-stop clinic

Bram Rook
Jaap Koedijk
Ilse E.B.M. Kroft
Elke M.G.J. de Jong

A version of this chapter was previously published in:J Wound Care. 2023 Feb 2;32(2):122-128.

ABSTRACT

Objective: Venous leg ulcers (VLU's) can impair patient quality of life (QOL) and have a significant impact on healthcare costs. Symptoms include pain and pruritis but can also lead to low selfesteem and sleep deprivation, which are often underestimated by physicians.

Method: We introduced a system in which patients with a VLU were examined and treated via a one-stop clinic. In this exploratory study, we evaluated the experiences of patients in this new setting using the Skindex-29 and conducting semi-structured interviews.

Results: A total of seven patients completed the questionnaires and interviews. The study found that younger patients had an impaired QOL due to symptoms disrupting activities of daily living. The cooperation between healthcare workers, the consistent execution of the treatment plan by different care providers and the close contact between staff and patients were appreciated by patients. Patients were positive about the continuous care provided by homecare workers at the patient's home, and experienced higher levels of attention to their illness.

Conclusion: The introduction of a one-stop clinic led to better insight and awareness among staff of patients' symptoms and complaints. More focus and time should be given to patient-oriented symptoms, which was highly appreciated by patients in this study. This could eventually lead to a reduction in the impairing effects of VLUs on patients' lives and healthcare costs due to fewer visits to the hospital.

INTRODUCTION

Venous leg ulcer (VLU) is a common chronic condition that has a tendency to heal slowly. Before the age of 45 years, the condition is rare, with an incidence ranging between 0.73–3.12 per 1000 personyears.[1–3] With increasing ageing, the incidence increases; in patients aged 75 years or older, the incidence is 8.3 per 1000 patient-years among women and 2.2 per 1000 patientyears among men.[4] The risk of recurrence of VLUs can be significantly high, with a rate of 57% within the first year.[3,5] VLUs are typically long-lasting and the percentage of VLUs that heal at 12 weeks is 44.1%, increasing to 80.0% within two years, while around 8.0% of ulcers remain unhealed after five years.[4,6] VLUs have a large impact on healthcare costs and on the quality of life (QOL) of patients. The cost of VLUs is a huge burden for national healthcare budgets of developed countries and annual direct medical costs are estimated to be $5527 USD per person per year.[3,7,8]

The most important cause of VLUs is chronic venous insufficiency (CVI).[9,10] CVI is caused by obstruction and damage caused by deep vein thrombosis (DVT) leading to venous hypertension.[9–11] This could eventually lead to a chronic alteration of tissue with necrosis and typical symptoms of CVI. VLU symptoms have a significant impact on the psychosocial wellbeing and social functioning of patients.[10,12,13] Sleep deprivation (as a consequence of pain), social isolation (due to reduced mobility) and smell can occur, along with lower selfesteem and reduced vitality.[10,13–15] Patients with a VLU often complain of (chronic) pain, itching and decreased mobility.[15]

The treatment of VLUs is often challenging. In addition to wound dressing and compression therapy, the treatment of any underlying disease, such as varicose veins, is important. In addition to this medical approach, every health professional should listen carefully to patients, as VLU is often a chronic disease greatly impairing their QOL. Treat 'the whole patient and not just the hole in the patient', is an important maxim, originally stated by Dr. Carry Sussman.[16] International guidelines have long paid too little attention to factors such as pain, lifestyle and QOL, which resulted in limited available information and data on how to organise ulcer care in a practice, patient-centred way.[17–20] This information could contribute to improving patient QOL, and increasing adherence to therapy and healing rates.[13,21,22] Now, greater focus is placed on QOL and patient-centred outcomes, including in scientific statements.[23,24]

Transforming to a new treatment strategy

In the Netherlands, standard care for patients with PTS and patients with VLUs is the responsibility of the GP.[4] If a wound does not heal well within six weeks or the GP is in doubt about the initial diagnosis, the patient is referred to a dermatologist. This system of care can cause delays as appointments and additional testing take place on different days, often within a week. After a number of outpatient visits, the diagnosis and a treatment plan are made. Subsequently, the patient has to visit the hospital each time for treatment of their wounds or underlying conditions by the dermatologist or wound care nurse, and other specialists dependent on their underlying condition.

In our hospital, we introduced a system to improve general ulcer care.[25] GPs referred all ulcer patients at an early stage. The main goal was to improve the efficiency and quality of the care path by introducing a one-stop clinic with specialised wound care nurses who would administer wound care in the home setting. This combination is unique in the Netherlands. In this new method, we strove to ensure that patients would visit the hospital only once for an integral diagnostic and therapeutic assessment. The most commonly performed tests included vascular function testing, such as ankle brachial pressure index, duplex ultrasound, blood tests and wound cultures. If no further diagnostic tests or invasive treatment were needed, wound care and compression therapy were performed and observed at patients' homes by specially trained wound care nurses from a range of homecare organisations. Already experienced nurses complete a one-year wound training course with various internships to become a specialist wound care nurse. These nurses were trained to work using an integrated approach, with particular attention given to the patient's preferences in order to improve outcomes, such as QOL and time to wound closure. If in-hospital treatment was advised, underlying conditions and wound care were first treated by dermatology nurses and, when appropriate, patients were referred back to their GP and homecare nurses. During clinic visits, patients were given further advice and encouragement to motivate them to manage their health themselves, to enable encouraging patient empowerment or a shared decision-making process.[26]

Aim of this research study

Previous research has already shown that a well-organised and evidenced-based homecare system, and that diagnosing and treating patients via a one-stop clinic can both be successful.[21,22,27,28] However, to the best of our knowledge, no research has been done yet on using a combination of homecare and an in-hospital onestop clinic to treat patients. In prior research, we already found improved medical

outcomes with our new method, such as a greater chance of faster wound closure.[25] Initially, one of the goals of this new method was to improve the quality of care for patients. We expected that this new approach would lead to increased satisfaction and better experiences for patients, resulting in an improved health-related quality of life (HRQOL). To explore this goal, evaluate patients' preferences and further improve the care provided, we studied the experiences of patients and healthcare workers with regard to this unique care process.

METHODS

Study design

This study used a combination of research methods including quantitative research using a questionnaire and qualitative research through interviews. The qualitative in-depth interview was chosen as the dominant research method. Before commencing the study, we performed a literature review on VLUs to map current knowledge and patient experiences. We also performed exploratory discussions with experts in the field to compile a topic list, the goal of which was to create a guideline for in-depth interviews with patients. For the literature review, we used international databases such as PubMed, Science Direct, Google Scholar and Wiley Online, with keywords within the field of venous ulcer wound care and QOL. Moreover, we studied the current national and international guidelines to explore awareness and understanding of patient QOL.

Research cohort

The research cohort consisted of patients >18 years of age with an active VLU who were seen at the one-stop clinic of the dermatology clinic of the Ziekenhuis Groep Twente (ZGT) after being referred by their GP. After a treatment plan was established, the patient's VLUs were treated by specialised nurses from a homecare organisation.

Qualitative and quantitative research methods

The topics for the semi-structured interviews were developed using the framework of the UK's National Health Service (NHS) for research on patients' experiences.[29,30] In addition, we also used those major topics advised by clinical experts (a copy of the questionnaire is obtainable from the authors on request). The questionnaire used for the quantitative aspect of the study was the Skindex-29,[31–33] although different tools for measuring HRQOL do exist.[34] The Skindex-29 is a dermatology-specific (health-related) QOL questionnaire that includes domain symptoms, emotional

wellbeing and social functioning, and is one of the few questionnaires validated for use in a Dutch population.[33,35] Answers were given on a fivepoint options scale, ranging from 'never' to 'always'. The individual domain scores and overall score were expressed on a 100-point scale, with higher scores indicating lower levels of HRQOL. At the one-stop clinic, new patients with a proven VLU were asked to participate in the study. When patients gave permission and informed consent was obtained to take part, the questionnaires were completed on that same day. A follow-up appointment was made to perform the interview after homecare was started. All questionnaires were completed before the interviews were started.

Ethical approval and patient consent

The medical ethics committee of the ZGT Hospital approved this study. All patients gave informed consent to take part in the study.

Analysis

We analysed the questionnaire using the cut-off values used for the official Skindex-29 as stated by Prinsen et al.,[35] subdividing the outcomes of the domains being examined into 'mild', 'moderate' and 'severe' categories. The interviews, in combination with the outcomes of the questionnaires, were analysed using a thick description method.

RESULTS

Patient characteristics

A total of eight patients with a new VLU were seen in the hospital during a two month period. However, one patient was excluded because he did not recognise his experiences in all statements. The mean age was 64 years (range: 48–78 years). Of the included seven patients, six were female and one was male. The duration of the interviews ranged from 25–55 minutes. All interviews were conducted at the patient's homes.

Analysis of questionnaires

As noted above, one patient (patient 2) indicated 'never' on all statements and indicated that he did not recognise his experiences in the statements. This patient was excluded before analysis of the questionnaire. Another patient indicated that his VLU had minimal impact including on social functioning in the last week prior to completing the questionnaire; therefore, the scores were low on all domains. The scores of all included patients in the analysis for each main domain are shown in

figure 1–3. For each domain, the total score is 100. The overall total score (figure 4) indicates the composite of all other domains and is suggestive of QOL.

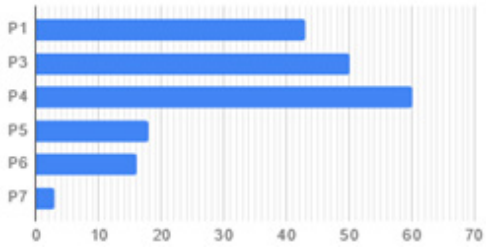


Figure 1. Scores Skindex-29 domain 'symptoms' (0-100)

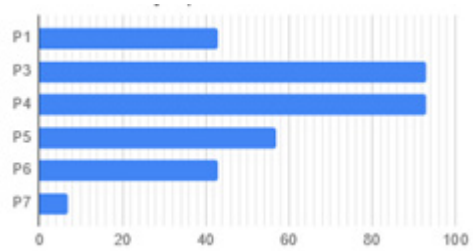


Figure 2. Scores Skindex-29 domain 'emotional wellbeing' (0-100)

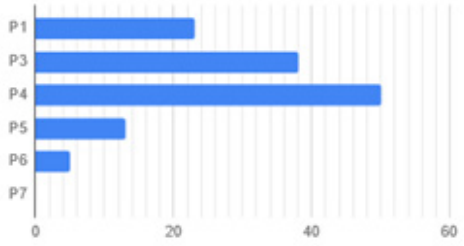


Figure 3. Scores Skindex-29 domain 'social functioning' (0-100)

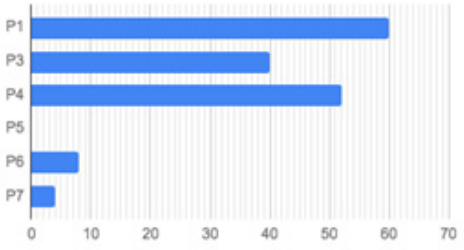


Figure 4. Scores Skindex-29 domain 'overall' (0-100)

Table 1 shows the cut-off values used by the Skindex-29 questionnaire. Patients who were relatively young scored 'high' on functioning (patients 1 and 4). In the interviews, patients with a high score on the domain symptoms stated that pain was the main impairing symptom, which impacted their daily routine, as seen in patients 3 and 4 who both scored 'severe' on symptoms, and 'moderate' and 'severe' on social functioning, respectively. Patients with a low total score stated that their wounds healed well and did not experience much pain, such as patient 7 (total score: 3/100).

Table 1. Cut-off values of Skindex-29[35]

Severity	Symptoms	Emotional well-being	Social functioning	Total score
Mild	≥39	≥24	≥21	≥25
Moderate	≥42	≥35	≥32	≥32
Severe	≥52	≥39	≥37	≥44

Analysis of interviews

Overall: The interviews showed that patients' experiences with the treatment path used in this study were mostly positive. Several patients indicated that they felt heard and understood, both at the one-stop clinic and at home, because of the specialised trained nurses who had additional knowledge of and who paid specific attention to their symptoms and complaints:

> *'They ask clearly about what you need, they really have personal attention for you. They check everything correctly and see if you can still handle it'.*

In addition, it was appreciated that there was sufficient time for extra explanation about the disease and treatment plan. Patients were enthusiastic about the recognition from the healthcare workers of their symptoms and feelings of psychological suffering as a consequence of their VLU. Patients were happy that a treatment plan was set up in only one morning or afternoon and with the prospect of further treatment in a home setting:

> *'You know very quickly where you stand, I like that people do not wait weeks and weeks and that you have to go there [the hospital] every time'.*

Referral: In the prehospital period, some patients were disappointed at the length of time until referral to specialised care in a hospital setting. For one patient the time until referral, which should be six weeks according to current Dutch guidelines, was exceeded. This patient did not feel taken seriously and lost trust in their GP:

'I think that the GP should refer much earlier if it cannot be resolved. Waiting two months for a wound to heal is a lot of time'.

Furthermore, some patients thought that, due to the introduction of the one-stop clinic, their GP was no longer interested in their wellbeing and healing of the condition. Some of the patients were disappointed about the distance to the one-stop clinic in the hospital because some of them had difficulty walking.

Communication: Several patient comments related to the good quality of communication:

'I think they have a lot of contact with each other [homecare and hospital]'.

The good accessibility of the dedicated nurses and the one-stop clinic was appreciated. This made communication easier and patients did not feel encumbered to ask questions. Additionally, healthcare workers were also enthusiastic about the communication between patients, nurses and the clinic. In cases where the dedicated homecare nurses needed expert help, they were easily able to refer patients back to the dermatologist or they could easily contact the hospital. A negative comment was made about the flexibility of homecare workers:

'Sometimes you are very dependent on the nurse to plan your day and they are not flexible in rescheduling appointments'.

Some appointments were not met, although patients often understood the nurse's busy schedule. In most cases, healthcare workers provided information flyers; however, none of the interviewed patients indicated they had read these information flyers. They stated that they would like to have had more information about their condition and the expected natural course of healing:

'I wanted to know a little more myself why it takes so long how come, and I do not hear much about that'.

Because this information was lacking, patients searched for information on websites or via family and friends.

Expert help: Patients commented that they were happy that specially trained nurses came to their homes to care for their VLU. There was a high degree of trust in the skills and knowledge of both the one-stop clinic and the dedicated homecare

nurses. A number of patients preferred being treated by dermatologists in the hospital, although this would mean more visits to the hospital. Healthcare workers also considered it important that patients felt heard and that they could offer expert care, such as wound dressings and patient education on the diagnosis and pain management. This could lead to greater patient trust in healthcare workers and might result in more adherence to therapy.[36–38]

Symptoms: Doctors, nurses and patients all indicated that pain was the major symptom that deserved the best attention. The consequences of pain, such as sleep deprivation and immobility, were often indicated by both healthcare workers and patients. Patients specified that, following wound healing, pain management was the most important aspect. Some patients needed maximum pain medication, which resulted in feelings of dizziness and fatigue:

> *'I had so much pain medication; more and more medication was prescribed, until those experienced wound nurses came, they were more attentive to the pain and how to deal with it'.*

Some patients required more information about pain management and dealing with the pain.

DISCUSSION

The aim of this unique exploratory study was to evaluate the experiences of patients on a new treatment pathway for VLUs. We therefore analysed the route from the GP, the referral process, the visit to the ulcer one-stop clinic, and the treatment by both the hospital and homecare organisations.

The results of the study were, in general, very positive. Patients reported that they were satisfied with the current treatment process. Both the one-stop outpatient clinic and the specialised homecare wound team were assessed as being pleasant and competent by all patients. Identifying new patient preferences was therefore difficult because patients indicated that they were not missing anything.

The current diagnostic process and treatment plan were preferable. However, there were a number of other issues raised by patients. Some respondents indicated that they preferred to visit a dermatologist due to a belief in their authority and that they had the most knowledge. This can be explained by the unfamiliarity and mistrust of

specialist wound care nurses. Other issues mentioned were not within the scope of this current study but were applicable to the GP or to care providers other than those of the one-stop outpatient clinic or the specialised homecare team. It is clear from the interviews that both patients and healthcare workers were satisfied with the current working method.

Because the natural course of a VLU varies for each patient and over time, it is difficult to collect all patient preferences and experiences through a single interview and in this small sample size. This chronic condition can manifest itself in various forms, resulting in simple discomfort in one patient to severe pain and a reduced QOL in another patient.[13,14] In some patients, the wound might be cured within three months, whereas in other cases, the duration to wound closure can last for two years.[1,4] The reported experiences may therefore differ due to patient characteristics, such as age, and the differing course or degree of influence of the disorder. This was also apparent during the interviews. In one patient, the VLU was discovered by accident and no discomfort was experienced other than the need for wound dressing. In another respondent, the wound had impacted her life for the previous two years. These experiences are in line with the findings of a systematic review examining symptoms and HRQOL of patients with VLUs.[15] The experienced impact on QOL also varies during the course of the disease.[13–15] For example, for a patient who presents with a large VLU that causes considerable pain and exudation, the wound has a different impact than when the wound is almost closed and only itches.

The Skindex-29 was chosen because it elaborates on different domain symptoms of patients and is one of the few suitable questionnaires validated for use in the Dutch speaking population. However, the Skindex-29 has its limitations.[39] The questionnaire only focuses on experiences in the past seven days. As a result, this questionnaire is not sensitive to the entire course of a VLU and its symptoms if it is only used once. A patient may have a well-healed ulcer, while two months previously, it had been a large wound and the patient was in great pain. Therefore, to obtain a clearer picture of the disease-specific QOL, the questionnaire should be taken at different times to be able to follow the course of a VLU. Other disease-specific questionnaires, such as the VEINES-QOL or the Cardiff Wound Impact Schedule, may be more suitable since these are disease-specific instruments, covering the particular characteristics of VLUs, and can be used over a longer period of time.[34,40,41] In contrast, use of the Skindex-29 is a good way for a nurse to evaluate the complaints of patients and creates an opportunity to discuss a patient's QOL. This could lead to earlier recognition of problems and implementation of

appropriate care. Therefore, we suggest that further research in a trial with a larger cohort and evaluation using questionnaires in this setting would ultimately improve the QOL of patients with a VLU. Using a questionnaire provides room to assess and discuss individual disease-burden and QOL, and provide greater attention to contributing factors. Further research should assess if routine measurement of QOL by questionnaires and addressing these outcomes with patients can improve medical outcomes and QOL.

In summary, we conclude that both patients and healthcare workers were satisfied with the one-stop outpatient clinic. Patients appreciated the logistical advantage of not having to travel to the hospital and the further professionalising of homecare by the efforts of specialised wound nurses. In order to maintain the optimal usability of this new care pathway, it is important to continue to guarantee continuous medical education in the field, accessibility of care for patients and patient involvement in decision-making in the longer term.[42] Wound nurses must gather enough competences and experience to continue to maintain their knowledge and skills to ensure the highest level of patient care. The cooperation between first-and secondline care providers is also important. As a result, using the one-stop outpatient clinic can increase both access to care and the quality of care.

Limitations

Our study was an exploratory qualitative research. This kind of research is often criticised for lacking validity and a weak reliability, for example due to response bias.[43] The type of research could have influenced the outcome and makes the interpretation of qualitative research challenging. In view of the exploratory nature of this study, conducting a mixed qualitative research using one-to-one interview and a questionnaire appeared the most appropriate. In addition, the small sample size is a major limitation, making it is questionable whether the results accurately reflect the opinion of all patients treated with this onestop clinic method. Due to the small number of patients, the generalisability of the results is also uncertain. The generalisability is even more limited because of the specific way the one-stop clinic is set up. However, since there are many different ways ulcer care is organised, including at regional and (inter)national level, the results of this study could contribute to the overall improvement of ulcer care.

Conclusion

Although this study was set up to explore patients' experiences and only a few patients were included, it nevertheless provides insight into the experiences of both patients and healthcare workers. The most important conclusions from this study are:

- The outcomes of the interviews were positive; in particular, the cooperation between healthcare workers, the consistent execution of the treatment plan by different care provides, and the close contact between staff and patients were appreciated by patients, which led to greater trust among patients in healthcare workers.
- Patients were satisfied with the quick diagnostic process at the one-stop clinic and follow-up.
- Patients preferred a comfortable and less stressful home treatment provided by specialised nurses rather than repeated consultations at hospital.
- Patients appreciated the time taken to explain the disease and therapy provided by the dermatologist and the hospital nurses, as well as the specialised homecare wound nurses.
- Pain was the most dominant symptom among patients with a VLU. Conducting an evaluation via a questionnaire would lead to insight into symptoms, and the offer of appropriate care.
- A disease-specific questionnaire is needed for patients with a VLU since the current questionnaires do not cover all domains and characteristics of hard-to-heal wounds such as VLUs.

REFERENCES

1. Nelson EA, Adderley U. Venous leg ulcers. BMJ Clin Evid. 2016 Jan 15;2016:1902.
2. Berenguer Pérez M, López-Casanova P, Sarabia Lavín R, González de la Torre H, Verdú-Soriano J. Epidemiology of venous leg ulcers in primary health care: Incidence and prevalence in a health centre–a time series study (2010–2014). *Int Wound J* 2019; 16(1):256–265.
3. Kolluri R, Lugli M, Villalba L, Varcoe R, Maleti O, Gallardo F et al. An estimate of the economic burden of venous leg ulcers associated with deep venous disease. *Vasc Med* 2022; 27(1):63–72.
4. Dutch Society for Dermatology and Venereology. Guideline venous pathology. [In Dutch] 2014. ''https://tinyurl.com/5n8vapfw'' [accessed 9 January 2023]
5. Finlayson K, Wu ML, Edwards HE. Identifying risk factors and protective factors for venous leg ulcer recurrence using a theoretical approach: a longitudinal study. *Int J Nurs Stud* 2015; 52(6):1042–1051.
6. Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. *Adv Wound Care (New Rochelle) 2018*; 7(3):77–94.
7. Guest JF, Ayoub N, McIlwraith T, Uchegbu I, Gerrish A, Weidlich D, et al. Health economic burden that different wound types impose on the UK's National Health Service. *Int Wound J* 2017; 14(2):322–330.
8. Ma H, O'Donnell TF Jr, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. *J Vasc Surg Venous Lymphat Disord* 2014; 2(4):355–361.
9. Comerota A, Lurie F. Pathogenesis of venous ulcer. *Semin Vasc Surg* 2015; 28(1):6–14.
10. Agale S. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. *Ulcers* 2013; 2013:article ID 413604.
11. Meissner MH, Moneta G, Burnand K, Gloviczki P, Lohr JM, Lurie F, et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg* 2007; 46(6 Suppl):S4–S24.
12. Roberts LN, Patel RK, Donaldson N, Bonner L, Arya R. Post-thrombotic syndrome is an independent determinant of health-related quality of life following both first proximal and distal deep vein thrombosis. *Haematologica* 2014; 99(3):e41–e43.
13. Hopman WM, VanDenKerkhof EG, Carley ME, Kuhnke JL, Harrison MB. Factors associated with health-related quality of life in chronic leg ulceration. *Qual Life Res* 2014; 23(6):1833–1840.
14. Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes* 2007; 5(1):44.
15. Phillips P, Lumley E, Duncan R, Aber A, Woods HB, Jones GL, Michaels J. A systematic review of qualitative research into people's experiences of living with venous leg ulcers. *J Adv Nurs* 2018; 74(3):550–563.
16. Hamm RL. Examination and evaluation of the patient with a wound. In: Text and atlas of wound diagnosis and treatment, 2e Ed. Hamm RL (ed). McGraw Hill, 2019
17. Franks PJ, Barker J, Collier M, Gethin G, Haesler E, Jawien A, et al. Management of patients with venous leg ulcer: challenges and current best practice. *J Wound Care* 2016; 25(Suppl 6):S1–S67.
18. Couch KS, Corbett L, Gould L, Girolami S, Bolton L. The International Consolidated Venous Ulcer Guideline Update 2015: process improvement, evidence analysis, and future goals. *Ostomy Wound Manage.* 2017 May;63(5):42-46.
19. Wittens C, Davies AH, Bækgaard N, Broholm R, Cavezzi A, Chastanet S, et al. ESVS Guidelines Committee. Editor's choice – management of chronic venous disease: clinical practice guidelines of the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2015; 49(6):678–737.

20. Mosti G, De Maeseneer M, Cavezzi A, Parsi K, Morrison N, Nelzen O, et al. Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. *Int Angiol* 2015; 34(3):202–218
21. Atkin L, Schofield A, Kilroy-Findley A. Updated leg ulcer pathway: improving healing times and reducing costs. *Br J Nurs* 2019; 28(20):S21– S26.
22. Harrison MB, VanDenKerkhof E, Hopman WM, Graham ID, Lorimer K, Carley M. Evidence-informed leg ulcer care: a cohort study comparing outcomes of individuals choosing nurse-led clinic or home care. *Ostomy Wound Manage* 2011; 57(8):38–45
23. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The post thrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2014; 130(18):1636–1661.
24. Kelechi TJ, Brunette G, Bonham PA, Crestodina L, Droste LR, Ratliff CR, et al. 2019 Guideline for management of wounds in patients with lower-extremity venous disease (LEVD). *J Wound Ostomy Continence Nurs* 2020; 47(2):97–110.
25. Rook B, Wikkerink M, Kroft EB. Evaluation of the introduction of the one-stop clinic and dedicated nurses for the ulcer cruris venosum care in the east of the Netherlands. *Phlebology* 2020; 35(1):27–28.
26. González-Consuegra RV, Verdú J. Quality of life in people with venous leg ulcers: an integrative review. *J Adv Nurs* 2011; 67(5):926–944.
27. Danner M, Hummel JM, Volz F, van Manen JG, Wiegard B, Dintsios CM, , et al. Integrating patients' views into health technology assessment: analytic hierarchy process (AHP) as a method to elicit patient preferences. *Int J Technol Assess Health Care* 2011; 27(4):369–375.
28. Manu CA, Mustafa OG, Bates M, Vivian G, Mulholland N, Elias D, et al. Transformation of the multidisciplinary diabetic foot clinic into a multidisciplinary diabetic foot day unit: results from a service evaluation. *Int J Low Extrem Wounds* 2014; 13(3):173–179.
29. Ahmed F, Burt J, Roland M. Measuring patient experience: concepts and methods. *Patient* 2014; 7(3):235–241.
30. NHS Institute for Innovation and Improvement. The patient experience book. NHS Institute for Innovation and Improvement, 2013
31. Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. *Arch Dermatol* 1997; 133(11):1433–1440.
32. van Cranenburgh OD, Prinsen CA, Sprangers MA, Spuls PI, de Korte J. Health-related quality-of-life assessment in dermatologic practice: relevance and application. *Dermatol Clin* 2012; 30(2):323–332.
33. Prinsen CA, Lindeboom R, Sprangers MA, Legierse CM, de Korte J. Health-related quality of life assessment in dermatology: interpretation of Skindex-29 scores using patient-based anchors. *J Invest Dermatol* 2010; 130(5):1318–1322.
34. Launois R. Health-related quality-of-life scales specific for chronic venous disorders of the lower limbs. *J Vasc Surg Venous Lymphat Disord* 2015; 3(2):219–227.e1–3.
35. Prinsen CA, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. *J Invest Dermatol* 2011; 131(9):1945–1947.

36. Shay LA, Lafata JE. Where is the evidence? A systematic review of shared decision making and patient outcomes. *Med Decis Making* 2015; 35(1):114–131.

37. Pinto RZ, Ferreira ML, Oliveira VC, Franco MR, Adams R, Maher CG, et al. Patient-centred communication is associated with positive therapeutic alliance: a systematic review. *J Physiother* 2012; 58(2):77–87.

38. Wounds International. International best practice statement: optimising patient involvement in wound management. Wounds International, 2016

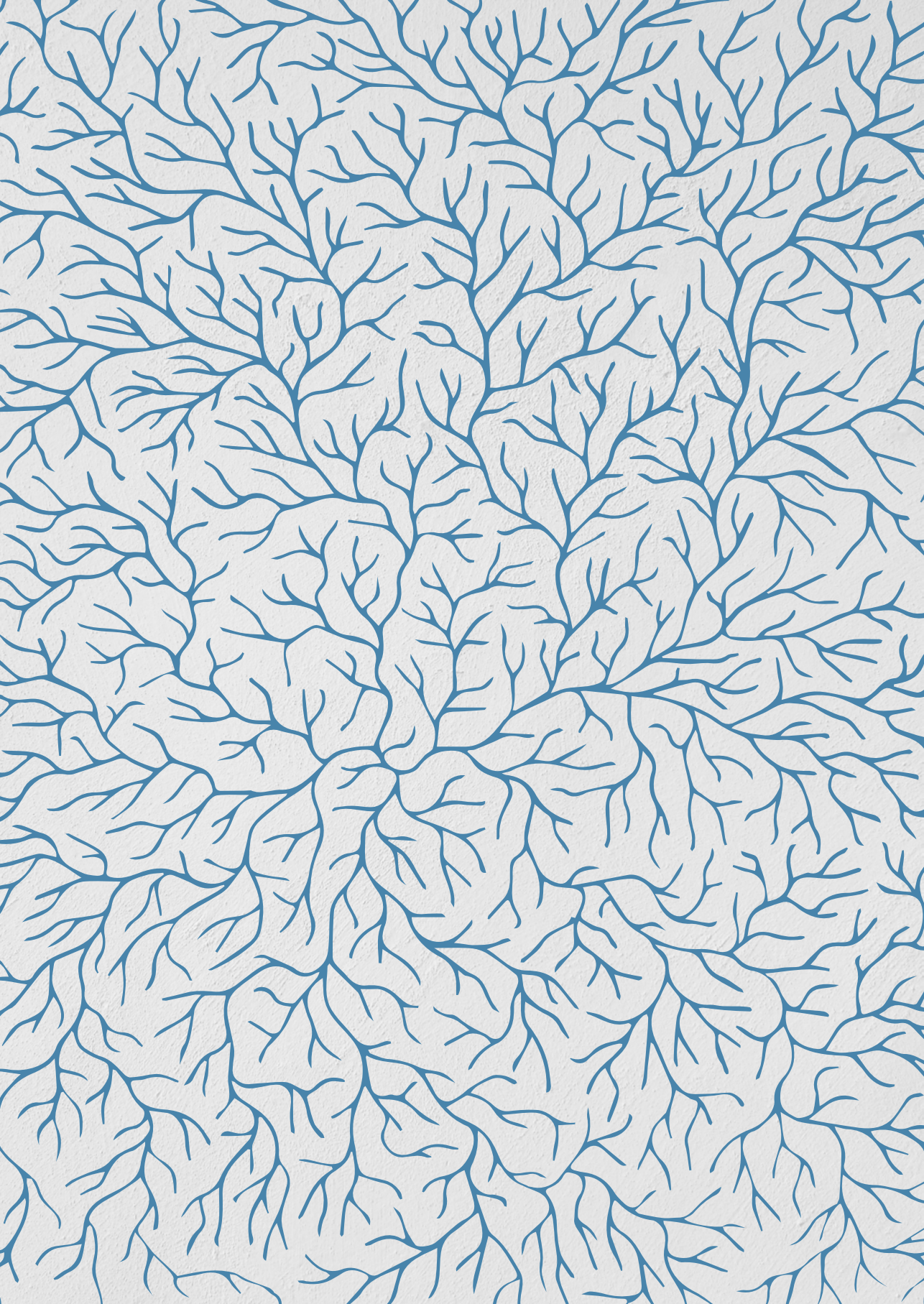
39. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol.* 2007 Dec;127(12):2726-39.

40. Bland JM, Dumville JC, Ashby RL, Gabe R, Stubbs N, Adderley U, et al. Validation of the VEINES-QOL quality of life instrument in venous leg ulcers: repeatability and validity study embedded in a randomised clinical trial. BMC Cardiovasc Disord 2015; 15(1):85.

41. Price P, Harding K. Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. Int Wound J 2004; 1(1):10–17.

42. Schäfer WLA, Boerma WGW, Schellevis FG, Groenewegen PP. GP Practices as a One-Stop Shop: How Do Patients Perceive the Quality of Care? A Cross-Sectional Study in Thirty-Four Countries. *Health Serv Res.* 2018 Aug;53(4):2047-2063.

43. Leung L. Validity, reliability, and generalizability in qualitative research. *J Family Med Prim Care* 2015; 4(3):324–327.



Chapter 4

The first comparative study of financial costs of treatment of venous ulcers at a Dermatology one-stop clinic followed up by specialized nurses in the community compared to 'standard care': A prospective pilot study

Bram Rook
Ilco W. Toebes
Ilse E.B.M. Kroft

A version of this chapter was previously published in: Journal of Phlebology & Lymphology, 2020, Vol 13, Issue 2, p1

ABSTRACT

Background: As our general population ages, the prevalence of venous leg ulcers (VLUs) is increasing. The disease consumes substantial healthcare resources and the financial burden of VLU care is increasing. Multiple implementations aimed at cost reduction have not yielded the expected results. Because we know that healthcare organisation can be an important target of cost reduction, we have created a new healthcare chain for diagnosing and treating VLUs.

Objective: To define and compare costs of treatment and evaluate cost-reduction in a one-stop clinic compared to standard care for VLUs.

Method: We followed prospectively all new patients with a single VLU. The research group consisted of patients of the one-stop-clinic and received homecare by dedicated wound care nurses. The control group received regular care. We investigated personnel costs and facility costs related to ulcer care.

Results: Research group consisted of 12 and control group of 8. The groups were similar in baseline characteristics. The mean total cost via the one-stop-clinic was €522.85 vs. €841.17 receiving standard care ($p=0.093$). After bootstrapping, we found an absolute difference of €125.39 (€618.97 vs. €744.36) ($p<0.001$); a cost-reduction of 16%.

Conclusion: An absolute cost-reduction of almost €300,- per patient and after bootstrapping a cost-reduction of 16% was found, indicating using one-stop-clinics and high educated wound care nurses could lead to cost-effective wound care.

INTRODUCTION

Venous leg ulcers (VLU) are a major burden for health care systems around the world, especially with an ageing population and an increasing prevalence.[1,2] It is estimated that 1% of Western health care budgets are compromised by venous ulcer care.[3,4] VLU's have a tendency to lead to chronic wounds[5] and therapy could take months.[6] Ulcers are invalidating and painful and could greatly reduce patient's quality of life (QOL) limiting daily activities, such as work. Ulcer healing has been shown to restore QOL.[7] VLE are often caused by underlying venous insufficiency and accounts for 70% of all leg ulcers.[1,8] Treatment consists of compression therapy and local wound treatment such as various wound dressings, debridement, excision of the ulcer or skin grafting[9-12] and aim for faster wound healing. Early treating venous insufficiency as underlying cause by superficial venous surgery can reduce the chance of a recurrent ulcer and result in faster ulcer healing.[13,14] The nature of the wound, ulcer size and duration determines the healing chances and therefore the type of treatment. Diagnosing and treatment by experienced and trained healthcare professionals is required.[15] Establishing a quick and correct diagnosis and initiating proper treatment will result in a shorter time of wound healing, restoring of QOL and simultaneously a cost reduction is expected.

At the end of the last century, specialized leg ulcer care clinics were introduced providing wound care. Studies investigating ulcer care already showed that diverse concepts such as centralizing ulcer care in a nurse-led clinic or an outpatient clinic improve time to wound healing an can reduce costs.[16-18] Though in these studies vital patients were included with a good ability to visits clinics, not representing the total population, which often suffer more comorbidity. Nevertheless, with increasing evidence that standardized based ulcer care is efficient in both financial as medical outcomes, primary ulcer care in the Netherlands is still within the responsibility of the general practitioner (GP), who can delegate the actual treatment to districts nurses, medical assistants and other therapists and might refer to a specialist when an chronic ulcer is developing.[19] Other studies showed that the organisation rather than the location of care is most important; using proper evidence based treatment standards for home care organisations would lead to similar outcomes with hospital care with similar outcomes and this even led to cost reduction.[20-22]

Aim of the study

With the continuing ageing of the population the prevalence of VLE increases. In the Netherlands, government policy focuses on the independence and self-reliance of older patients in the home situation and therefore ulcer care too is preferably

provided at home. In line with the aforementioned and the recognition of value-based medicine, we wanted to create an unique organisation structure in with both a centralized ulcer care clinic and a proper functioning home care treatment method were combined. Despite aforementioned evidence of early treatment of underlying causes, the system of ulcer care has not been changed for years. Therefore we set up a new system of uniting previously proven different healthcare concepts. In this situation, at an early stage of the disease, a diagnosis was made in one day in the hospital outpatient clinic and subsequently home care organisations delivered evidenced based (dedicated nurses) care at home and, if necessary, additional treatment was given at the hospital. The system is shown and explained in figure 1. At the Dermatology department of the ZGT hospital in the East of The Netherlands we investigated if implementation of the new set up would be cost-effective. Our hypothesis was that this new method would lead to cost reduction in comparison with the standard way of care in the Dutch system of venous ulcer care. With this pilot study we could furthermore explore which cost items exists, therefore creating a foundation for further research. The primary research question of this pilot study is: is there a difference in primary health-care costs (in euros) between the new method at the one stop clinic compared to the standard ulcer care?

METHODS

Study design

Little prior research has so far been conducted to investigate the financial costs of different systems of VLU care. Hence, because of this, no weighted decision could be taken for required estimates for a power analysis research. So we conducted a small prospective pilot study to investigate our hypothesis and create a foundation for further research. Therefore we used the standard treatment design in the Deventer Hospital, which is representative for VLU care in the Netherlands. This system is shown in figure 2. Secondary outcomes were number of visits, ulcer size, time to wound closure, time per visit, cost of supplies and general overhead cost per patient per visit.

Data collection

Financial costs were calculated through the Simplified Activity Based Costing (S-ABC) method to calculate actual costs per patient (figure 3). This method is known to be a more reliable method compared to volume based costing. Each event is an 'activity' and for each activity a specific cost item is created. The S-ABC uses less cost items compared to the ABC method and therefore is more useful

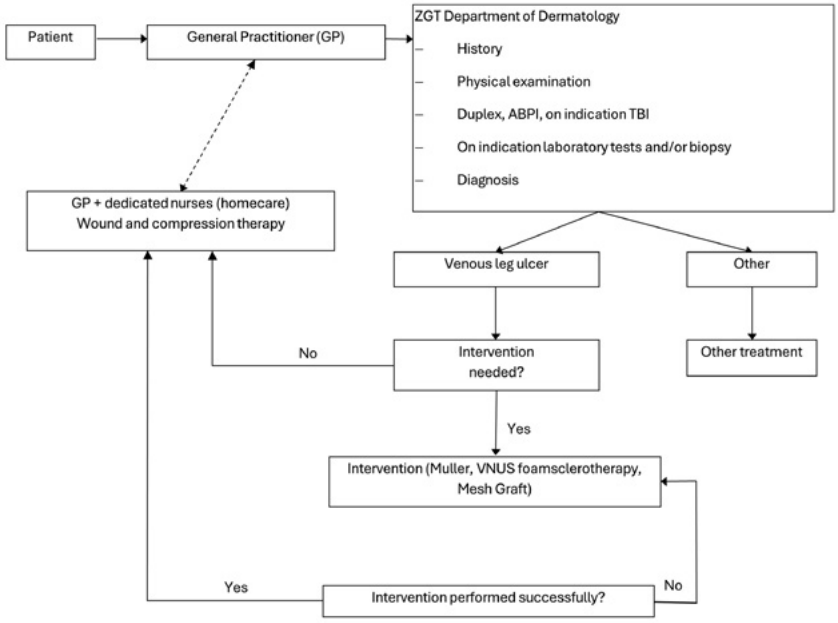


Figure 1. Overview of the one stop clinic. GP refers patients the Dermatology department for an assessment in an early stage of the ulcer. During the 'first consult' the anamneses, physical examination, vascular research and the diagnosis are performed in one day. Sometimes when laboratory test and/or biopsy is taken, the diagnosis comes later. In the homecare setting, dedicated nurses can contact de Dermatology department at all times with questions for a known patients, therefore improving quality care and if necessary, a fast assessment in the hospital if needed. *ABPI: ankle-brachial pressure index; TBI: toe brachial index; VNUS: endovenous radiofrequent ablation*

to implement in a pilot study. To determine the activities, all factors relating to financial cost of VLU care, were identified with both qualitative and quantitative research. For qualitative research health care professionals were interviewed to collect data as wages, total working hours and average costs of care-packages for the funding of diagnosing and treating VLU.

To calculate the actual costs per patient we first reviewed all patients' records to collect data such as patient characteristics and data about wound size, time to wound closure, number of visits and time per visit. Time for wound closure was the time between first visit up to last consult of any healthcare professional involved the treatment process. At last, facility (overhead) costs were identified using the annual reports of both hospitals, which were divided by all patients in the hospitals as in line with the S-ABC method. In this trial we focused only on costs of logistics and on organisational level, we did not add costs as bandaging and other wound care products as this was beyond the scope of this trial. However, these costs are

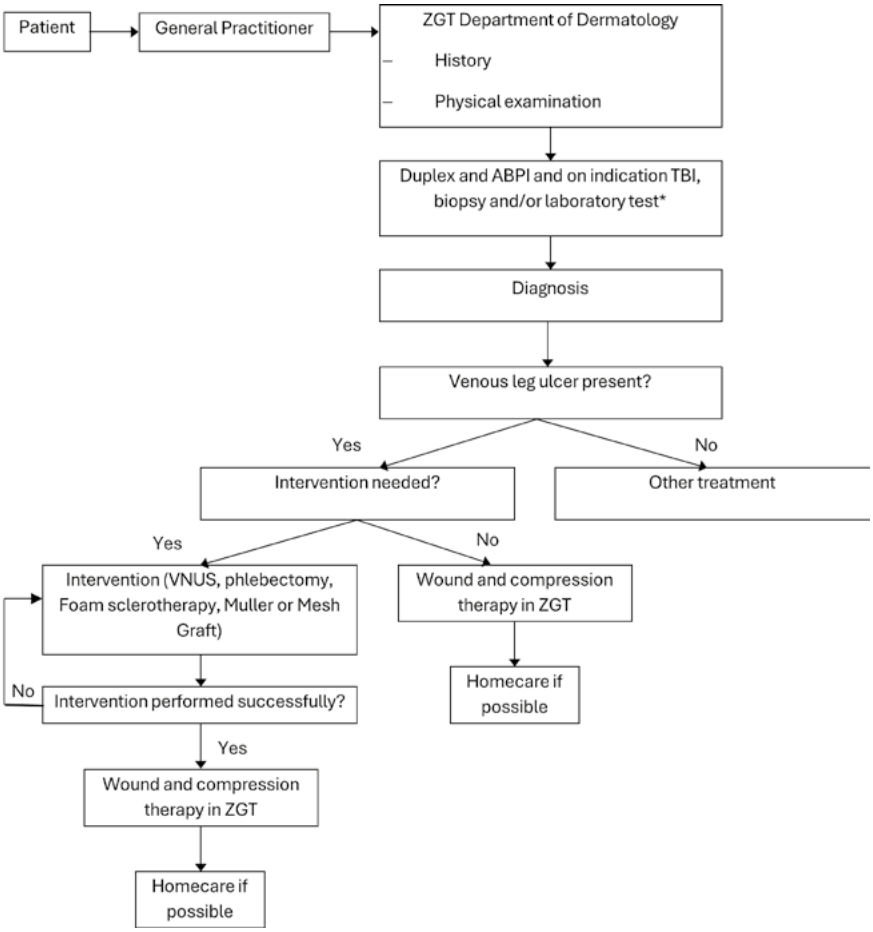


Figure 2. Overview of the old method. GP refers patients to hospital if there is not enough healing trend after 2 months or if there is a high suspicion on a specific cause of the ulcer. In this situation more visits were needed before a diagnosis was set. The patient receives care with the hospital/dermatologist as main physician. *ABPI: ankle-brachial pressure index; TBI: toe brachial index; VNUS: endovenous radiofrequent ablation*

Total personal costs per patient are calculated by the following formula, based on the S-ABC method:

Personal costs patient =∑(number of visits [function]× hourly wage [function]60 × number of minutes)

Total facility costs per patient are calculated by the following formula, based on the S-ABC method:

Facility costs per patient = ∑ ((depreciation of fixed assets + additional operating costs)/((total number of patients hospital)/365) x number of visits hospital)

Figure 3. Calculation of costs based on the S-ABC Method

known to be a major part of the total costs of VLE and are too subject of debate in reduction health care costs.

Patient selection

A random sample using a randomisation program was conducted from all patients with an VLE attending ZGT and Deventer Hospital in the period between January 2016 and February 2016. Due to the pilot study design this was not a formal randomized controlled trial and we included a limited amount of patients. All included patients have had a new VLU. We followed this patients till the wound was healed. The patient did not require any further treatment. All patients were 18 or more years of age. Inclusion criteria for the research group include new ULV patients of the one stop clinic at the ZGT who were treated in the home setting by dedicated home care nurses from two local homecare organisations between January 2016 and February 2017. The control group consists of patients according to the standard of care for VLU in the Deventer Hospital. Patients were excluded if they had any other cause of the ulcer after additional investigation (e.g., Doppler, ankle-brachial pressure index; toe brachial index) such as mixed ulcer, arterial, decubitus, diabetic, vasculitis, oncological, pyoderma gangrenosum, arteriolar or erysipelas or a recurrent ulcer and multiple ulcers.

Statistics analysis

The groups were normally distributed, and while we did not know in advance which pathway would be less expensive, we used unpaired, two sided t-tests to compare both groups. Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR); categorical variables as counts with corresponding percentages. Descriptive data is shown in tables and charts. Since the small number of the sample sizes, we used the bootstrapping method as statistical analysis for a better understanding of the results.

RESULTS

Twelve patients were included in the research group. Eight patients were included in the control group. All patients (100%) were referred to the clinic by a GP, none of the patients was admitted for in-hospital treatment. Therefore no invasive interventions were performed in any patient. Baseline characteristics of all individual and combined groups are shown in table 1. The groups did not alter significantly regarding baseline characteristics. In figure 4 and 5 the mean number of visits per healthcare professional in the hospital and at home are described.

Table 1. Baseline characteristics of all groups.

Variable	CarrintReggeland	ZorgAccent	ZGT (CarintReggeland + ZorgAccent)*	Deventer Hospital	P-value (ZGT vs. Deventer Hospital)**
Sex (M/F), *n* (%)	5 (71)/2 (29)	4(80)/1(20)	9(75)/3(25)	4(50)/4(50)	0.296
Mean age, *years* (SD)	4(80)/1(20)	67.16 (12.69)	62.08 (13.81)	69.88 (11.54)	0.190
Mean time of treatment, *days* (SD)	73.00 (72.47)	126.20 (135.97)	95.17 (101.68)	78.50 (38.96)	0.615
Mean ulcer size, cm^2 (SD)	2.07 (1.81)	5.36 (8.69)	3.15 (4.19)	4.65 (3.84)	0.414

M: male; F: female; SD:Standard deviation ZGT: Ziekenhuisgroep Twente. P-values that are significant (P<0.05) are reported bold. * research group; **control group

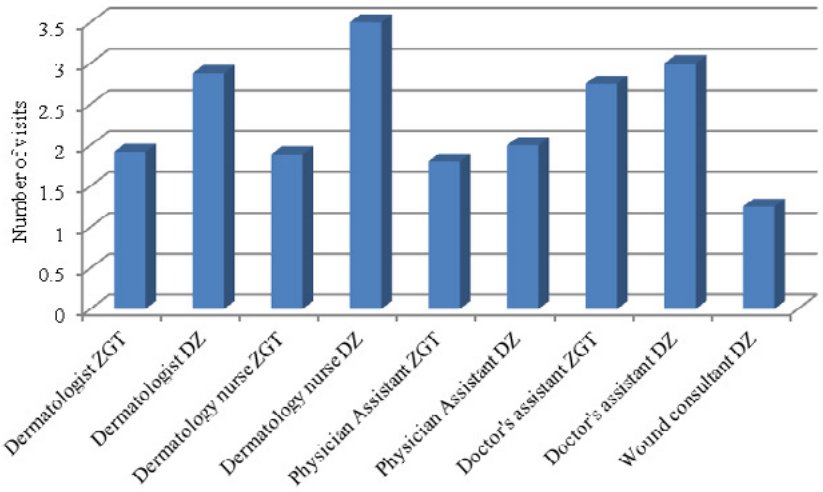


Figure 4. Mean number of visits per healthcare professional at the hospital.

We converted all visits with the actual time per visit, per healthcare professional, with their corresponding wage and calculated the mean costs per function and per institution and eventually the mean total costs of each patient. The results are listed in figure 6 and 7. For almost each type of healthcare professional the mean costs per patient are more expensive in the control group in comparison with the research group, often due to less visits. Facility costs per patients for each hospital were calculated for the year 2016 for the total number of visits for each hospital; € 1.96 (research group) vs. € 1.07 (control group). The mean total costs per patient with an VLU in this study were based on the total personnel costs and the facility costs. The mean total cost of a treatment with the new method was € 522.85 vs. € 841.17 in the standard way of ulcer care (p=0.093) (figure 4). The mean number of visit in the hospital was 5 in the research group and 9 in control group (p=0.177). The mean number of visits by nurses was 10 in the research group compared to 17 visits in the control group (p=0.236). The mean number of days of treatment was in the research group 96 days, whereas in the control group the mean number of days of treatment was 79. Due to the small number of total sample size, we used the bootstrap method for extending the total sample size to a fictional 1000 patients in both groups. Although this method does not compensate up for the small sample size, the bootstrapping method shows more reliable results instead of using the original sample size, since it resulted in wider interval between the upper and lower border of the 95% confidence interval compared to the initial samples. Statistical analysis after bootstrapping the difference showed significant differences between the groups for mean total costs € 618.97 (research group) vs. (€ 744.36 (control group), P<0.001.

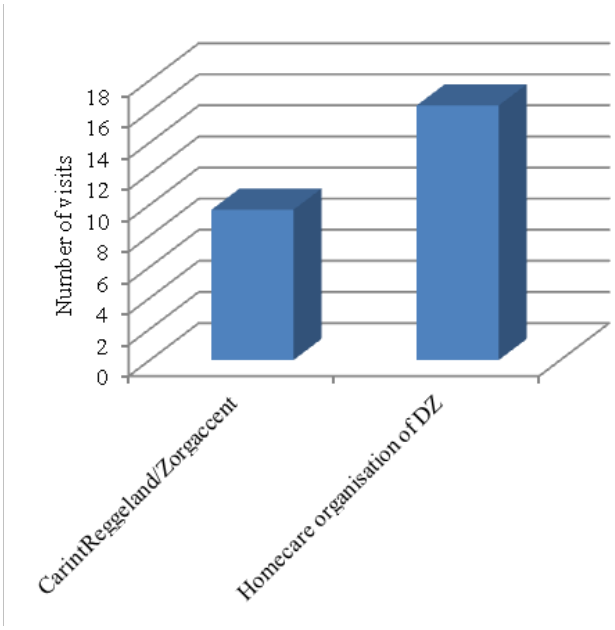


Figure 5. Mean number of visit of per healthcare professional at homecare organisation.

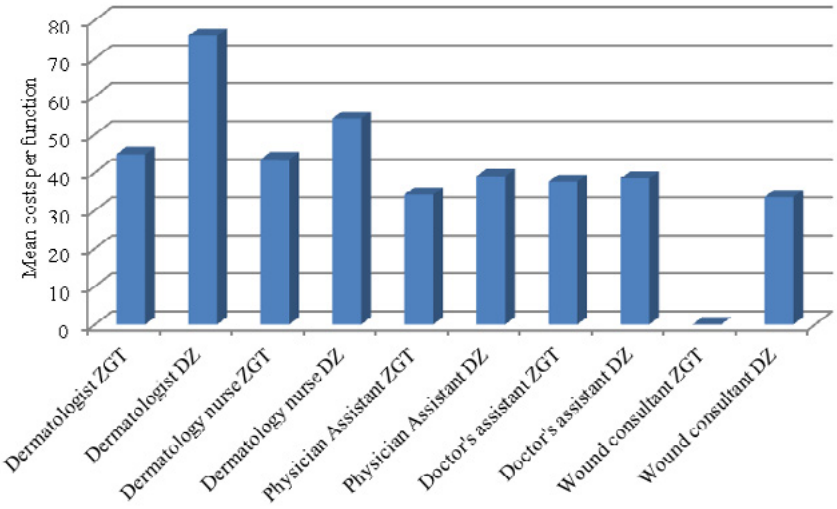


Figure 6. Mean costs per function per patient at the hospital.

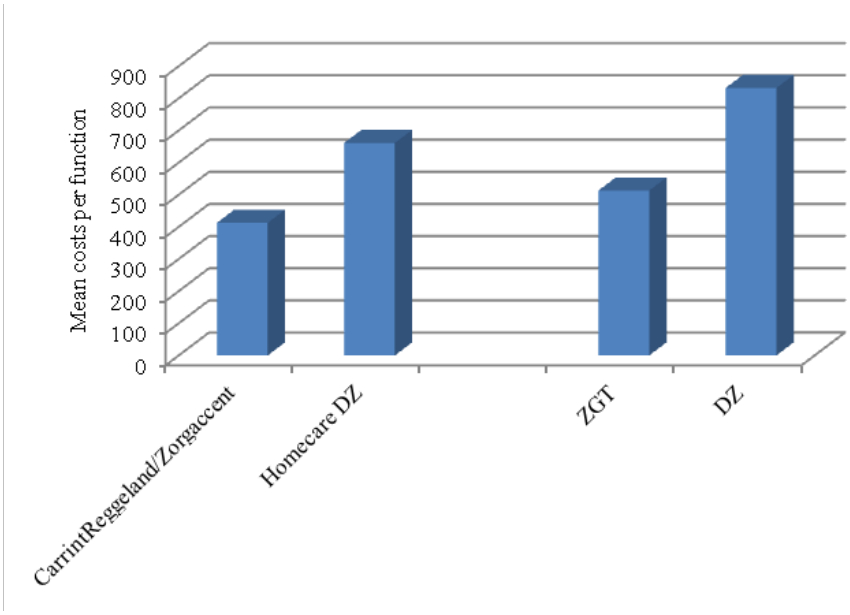


Figure 7. Mean costs per homecare organisation and mean costs in research groups ZGT (ZGT hospital + CarrintReggeland/Zorgaccent) and DZ (Control group: homecare Deventer Hospital + Deventer Hospital).

DISCUSSION

In this trial we compared the difference in costs between the new treatment pathway and the standard way of VLU care. The one-stop clinic was introduced to decrease the number of visits to the hospital by setting a fast and correct diagnosis, set up a treatment plan in the hospital and, if possible, continue the ulcer care in home setting by specially trained wound care nurses. After statistical analysis with bootstrapping method we found an absolute difference of € 125.39 (€ 618.97 for one-stop clinic vs. € 744.36 in usual care), which is more than 16% reduction, $P<0.001$. These number indicate that this innovative new concept of combining centralized care for VLE in combination with a standard and evidenced based treatment in home setting is cost effective and saves resources. In an ever increasing population with patients physically incapable of frequent visiting an outpatient clinic this is an important issue in organising health care.

Since the design of this first unique pilot study, large-scale follow-up research in a prospective design can provide a better insight into the differences and correlations of all costs concerning VLU care. Our study showed that the absolute number of visits to the hospital and visits by dedicated wound care home care nurses at home was less compared to the standard care. The time for wound healing was longer compared

to the control group, whereas we expected this to be less since the proper and fast initiation of treatment by the one stop clinic, however, this is a secondary outcome for which the study was not powered. There was not a difference in mean ulcer size between both groups which could explain the difference. However, prior research investigating time to wound healing showed that centred care would lead to less time to wound healing, which is not corresponding with our current results.[22] In the new method, the dedicated home care nurses are specifically trained to monitor and treat VLU, which could explain the smaller number of visits in the research group. In our study we determined the costs by using the S-ABC method by collecting all direct costs of personnel, care package and overhead costs. Follow-up research should attempt to gather the costs of all domains, such as wound material and costs of additional invasive treatment. We calculated the personnel costs with total time of care with the wages of different types of health care professionals. In another study investigating the costs of VLU care, the total personnel costs were based on a total working hours per month (150 hours) and there was an additional increase of almost 30% for profit purposes.[24] We choose only to calculate the exact actual costs and not add any value for profit benefits. The purpose of this study was to evaluate methods for improving health care and cost effectiveness in wound care. Known factors, such as wound size, duration of the wound, prior history of ulcer are negatively reduction wound closure.[25] Other aspects as proper indications for and time till referral to a specialist, the amount and length of compression therapy and the use of various wound dressings are still topics of current research. Further research combining these aspects in ulcer care is necessary for gaining insight and indicate processes where improvement could be achieved.

Limitations

A major limitation is the small number of patients. This is due its pilot design and being the first unique study combining a one stop clinic with an integrated specialized home care system. Since the pilot design of the study the results are indicative for a cost reduction by implementation of this system of ulcer care. While bootstrapping as methodologically method shows more reliable results for statistical purposes, it does not compensate up for the small sample size. Increasing the sample size using bootstrapping provided insight into the cost savings that can be achieved with a larger population. We carefully calculated the cost item of each type of health care professional involved in VLU care. The costs of separate diagnostic investigations such as duplex ultrasound were not taken into account as we assumed these costs were similar for patients during the diagnostic process and are covered under overhead costs. Since none of the patients was treated for underlying causes of venous insufficiency, no costs of invasive treatment were collected. For practical reasons the overhead costs of the organisation have been divided proportionally among all patients in the hospital

for the year 2016 for both hospitals. This was in our opinion the most reliable method to include hospital overhead costs in this pilot study. Further analysis of indirect costs such as travel time (both for nurses as patients), socio-economics costs as missed working days was beyond the scope of this trial. Although some (in)direct costs were missed out, we think this study shows an adequate overview of the logistics and organisation costs in both the one stop clinic and the standard way of care for venous ulcer care. Since this study was conducted in one specific region with only two different hospital settings, this introduces bias which limits its generalizability. The results are nonetheless an indication that one-stop clinics and dedicated nurses could lead to cost saving and are beneficial in the context of financial reasons.

Conclusion

The prevalence of patients with VLUs is increasing with an ageing population with more comorbidity. VLUs have a substantial economic impact on health care systems and are often a chronic condition with an invalidating impact on patients' lives. We initiated a new innovative method of treating VLUs by implementing a one-stop clinic at the outpatient clinic of the Dermatology department. In one visit, the medical history, physical examination and additional (vascular) examinations were performed. Furthermore we trained dedicated wound care nurses supplying ulcer care at patients' homes. To evaluate the cost-effectiveness of new strategy, we conducted a cost analysis study. We investigated all personnel costs and facility costs in relation to the ulcer care. The average cost of a treatment with the new method was € 522.85 vs. € 841.17 in the standard way of ulcer care (p=0.093). After bootstrapping the sample size since the small initial number of patients, we found an absolute difference of € 125.39 (€ 618.97 vs. € 744.36) (P<0.001), which is more than 16% cost-reduction.. This first pilot study shows that cost reduction is possible by introduction of new health care concepts. These outcomes must not be generalized for all ulcer care, but are an indication that one-stop clinics and well organised specialised home ulcer care could lead both to health care improvements be beneficial in the context of and economic consequences by cost saving.

Acknowledgements

The authors want to thank R. Houwing (Dermatologist Deventer Hospital), M. Wikkerink (PA wound/skincare Carintreggeland), R. Wijnsma (medical assistant Dermatology ZGT), I. Kops Hagedoorn (medical assistant Dermatology Deventer Hospital) and A. Haagberg (wound nurse Carintreggeland) for their help in collecting and analysing the data in the files.

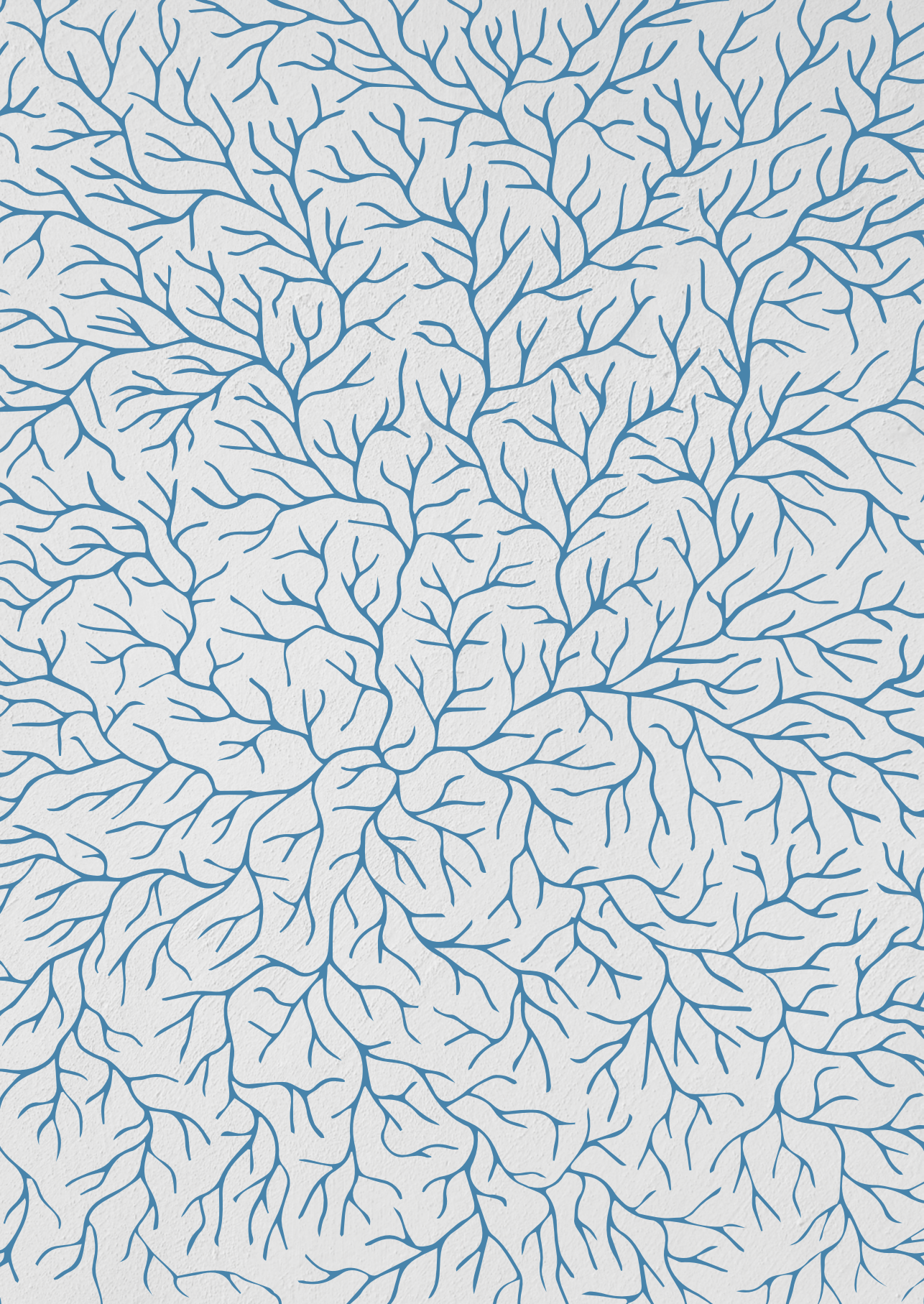
REFERENCES

1. Agale SV. Chronic Leg Ulcers: Epidemiology, Aetiopathogenesis, and Management. *Ulcers*. 2013, Article ID 413604, 9 pages.
2. Anderson I, King B. Mixed aetiology leg ulcers. *Nurs Times* 2006;102;45, 47, 49-50.
3. Guest JF, Ayoub N, McIlwraith T, Uchegbu I, Gerrish A, Weidlich D, et al. Health economic burden that different wound types impose on the UK's National Health Service. *Int Wound J* 2017;14:322–30.
4. Ma H, O'Donnell Jr TF, Rosen NA, Iafrati MD, The real cost of treating venous ulcers in a contemporary vascular practice. *J Vasc Surg Venous Lymphat Disord.* 2014 Oct;2(4):355-61.
5. Nicolaides AN, Allegra C, Bergan J, Bradbury A, Cairols M, Carpentier P, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. *Int Angiol*. 2008 Feb;27(1):1-59.
6. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. *N Engl J Med* 2006;355:488–98.
7. Kahle B, Hermanns HJ, Gallenkemper G. Evidence-based treatment of chronic leg ulcers. *Dtsch Arztebl Int*. 2011 Apr;108(14):231-7.
8. Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care.* 2003 Nov;16(6):305-16
9. Nelson EA, Adderley U. Venous leg ulcers. *BMJ Clin Evid.* 2016;2016:1902.
10. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. *Cochrane Database Syst Rev*. 2012 Nov 14;11(11):CD000265
11. V. Montfrans C, De Boer EM, Jansma EP, Gibbs S, Mekkes JR, Van der Vleuten CJM, et al. Behandeling van patiënten met een veneus ulcus cruris. Wat als compressietherapie alleen niet meer helpt? *Nederlands Tijdschrift voor Geneeskunde.* 2013;157:A5647.
12. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev*. 2013 Jan 31;(1):CD001737
13. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, et al. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. *N Engl J Med. 2018* May 31;378(22):2105-2114.
14. Howard DP, Howard A, Kothari A, Wales L, Guest M, Davies AH. The role of superficial venous surgery in the management of venous ulcers: a systematic review. *Eur J Vasc Endovasc Surg.* 2008 Oct;36(4):458-65.
15. Van Mierlo-van den Broek PA, de Laat HE. Verkenning wondbehandeling in Nederland. In opdracht van CVZ. Nijmegen; 2012: 1-204.
16. Manu CA, Mustafa OG, Bates M, Vivian G, Mulholland N, Elias D, et al. Transformation of the multidisciplinary diabetic foot clinic into a multidisciplinary diabetic foot day unit: results from a service evaluation. *Int J Low Extrem Wounds.* 2014 Sep;13(3):173-9.
17. Gottrup F, Holstein P, Jørgensen B, Lohmann M, Karlsmar T. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. *Arch Surg.* 2001 Jul;136(7):765-72.
18. Rondas AALM, Schols JMG, Halfens RJG, Hull HR, Stobberingh EE, Evers SMAA. Cost analysis of one of the first outpatient wound clinics in the Netherlands. *J Wound Care.* 2015; 24(9): 426–436.
19. Van Hof N, Balak FSR, Apeldoorn L, De Nooijer HJ, Vleesch Dubois V, Van Rijn-van Kortenhof NMM. NHG-Standaard Ulcus cruris venosum (Tweede herziening). *Huisarts Wet* 2010:53(6):321-33.

20. Harrison MB, Van Den Kerkhof E, Hopman WM, Graham ID, Lorimer K, Carley M. Evidence-informed Leg Ulcer Care: A Cohort Study Comparing Outcomes of Individuals Choosing Nurse-led Clinic or Home Care. *Ostomy Wound Manage.* 2011 Aug;57(8):38-45
21. Harrison MB, Graham ID, Lorimer K, Friedberg E, Pierscianowski T, Brandys T. Leg-ulcer care in the community, before and after implementation of an evidence-based service. *CMAJ.* 2005 May 24;172(11):1447-52.
22. B. Rook, M. Wikkerink, E. Kroft. Evaluation of the introduction of the one-stop clinic and dedicated nurses for the ulcer cruris venosum care in the east of the Netherlands. *Phlebology.* 2020 Feb;35(1):27-38.
23. Westerdijk M, Zuurbier J, Ludwig M, Prins S. Defining care products to finance health care in the Netherlands. *Eur J Health Econ.* 2012 Apr;13(2):203-21.
24. Baptista CMC, Castilho V. Cost survey of procedure with Unna boot in patients with venous ulcer. *Rev Lat Am Enfermagem.* 2006 Nov-Dec;14(6):944-9.
25. Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med.* 2000 Jul;109(1):15-9.

PART TWO

Treatment and prevention of post-thrombotic syndrome



Chapter 5

The value of compression therapy following deep venous thrombosis

Yee Lai Lam
Bram Rook
Ilse E.P. Jansma
Marieke Kruip
Marie Josee E. van Rijn
Catherine van Montfrans

A (Dutch) version of this chapter was previously published in: Ned Tijdschr Geneeskd. 2020;164:D3622

ABSTRACT

Post-thrombotic syndrome (PTS) is the most frequent and potentially invalidating long-term complication of deep vein thrombosis (DVT). Symptoms of PTS can invalidate quality of life severely. PTS is expected to occur in 20-50% of patients without compression therapy, often within the first two years. Compression therapy is advised to prevent PTS and reduces the risk with 38%. After diagnosing DVT, compression therapy should be initiated as early as possible to reduce the risk of residual venous obstruction and therefore reduce the risk of PTS. It is recommended to routinely assess patients for signs of PTS after six months after an acute DVT, using medical history and physical examination in combination with the Villalta score. An individualized duration of compression therapy of less than two years should only be considered if an experienced and skilled physician detects no signs of PTS during follow-up. For a long time it was not clear what the duration of compression therapy should be, which led to the common practice of wearing compression stockings for two years. In 2018, the Dutch-Italian IDEAL study was published.[1] This study showed that in more than half of the patients with DVT without signs of PTS in two consecutive visits with at least three months interval, compression therapy could be discontinued earlier. PTS did not develop more frequently compared the baseline group that was prescribed two years of compression therapy. In this article we provide tools for recognising PTS based on history, symptoms and physical examination. We then discuss the effectiveness and duration of compression therapy to prevent PTS.

Post-thrombotic syndrome

Without compression therapy, post-thrombotic syndrome (PTS) is expected to occur in 50% of patients, with a severe PTS in one-fifth of these patients.[2] PTS can also occur after an asymptomatic deep vein thrombosis (DVT), which is important to remember while analysing legs with symptoms of PTS in patients without a history of DVT. It usually develops within the first two years after DVT, but sometimes after a longer period of time.[3] The pathophysiology is complex, multifactorial and not yet fully understood. The main factors include obstruction of the veins and/or reflux due to damaged valves, which both lead to venous hypertension, eventually leading to tissue changes and PTS. Five to ten percent of all patients with TPS have a form of severe PTS that mainly occurs with persisting venous obstruction of the common femoral vein or more proximal venous obstructions. Of the complications of DVT, PTS gives the most complaints in the long-term.[4]

Symptoms and signs

The symptoms of PTS range from a tired and heavy feeling in the leg after standing or walking, to pain, cramps, itching, and paraesthesia. The distinction between arterial, neurological, or orthopaedic causes can be made by asking whether the symptoms improve when the leg is elevated. In severe PTS venous claudication may occur, this a feeling of tightness or intense pain in the leg during walking that decreases in severity when the leg is elevated.

Physical examination

During physical examination the affected leg can be swollen and a difference in circumference between both legs can be observed. Other signs of chronic venous insufficiency can be observed, including edema, eczema and / or hyper pigmentation, lipodermatosclerosis, atrophy blanche and / or a (cured) ulcer (figure 1). It is important not to limit the physical examination to the legs. The presence of varices on the abdomen, typically in the pubic area or on the flanks, may indicate an iliac or ilio-caval venous obstruction. In such cases this is an indication to conduct further investigate thrombosis in this region.

Predictors and measuring instruments

The two most important predictors of PTS are an extensive proximal thrombosis in the iliofemoral segment and an prior ipsilateral DVT. Other risk factors of PTS include preexisting chronic venous insufficiency, obesity, inadequately anticoagulation treatment with vitamin K antagonists, older age and residual venous obstruction.[3] Some of these risk factors are included in the SOX-PTS prediction score for PTS, which is currently being validated.[5]

Figure 1. Signs of chronic venous insufficiency Photos of the affected foot from three patients with post-thrombotic syndrome. (A) Venous leg ulcer on the lateral malleolus, surrounded by white atrophy (atrophy blanche) within a palm-sized area of erythema. (B) Healed venous leg ulcer on the medial malleolus with local eczema and hyperpigmentation. (C) Medial malleolus showing hyperpigmentation.

There is no gold standard for diagnosing PTS. There are several scoring systems, the Villalta score being used most frequently (table 1) and advised to diagnose and classifying PTS in clinical studies.[6-8] The Villalta score consists of a combination of clinical symptoms and signs during physical examination. According to the International Society on Thrombosis and Haemostasis, PTS is present when the Villalta score is greater than 4 at any moment at least 6 months after a prior DVT.[8]

Table 1. The Villalta scoring system

score-item	**score***			
symptom	**absence**	**mild**	**moderate**	**severe**
pain	0	1	2	3
cramps	0	1	2	3
heaviness	0	1	2	3
paraesthesia	0	1	2	3
pruritus	0	1	2	3
clinical signs				
pretibial edema	0	1	2	3
skin induration	0	1	2	3
hyperpigmentation	0	1	2	3
erythema	0	1	2	3
venous ectasia	0	1	2	3
pain on calf compression	0	1	2	3

PTS = post-thrombotic syndrome

* Each item is scored as 0 (absence), 1 (mild), 2 (moderate) or 3 (severe). Total score 0-4: no PTS; 5-14: mild to moderate PTS; > 14: severe PTS. Presence of venous ulcer automatically confers the highest severity (severe).

Prevention of PTS

Because there is no optimal treatment for PTS, prevention is important. Besides anticoagulation therapy, compression therapy reduces edema, accelerates venous blood flow and improves venous pumping function.[9] In addition, it stimulates local fibrinolysis.[10] In case of patients having edema, compression therapy is first applied in the form of a multi-layered dressing (figure 2A) or an elastic stocking with strength and with sufficient reduction from the edema, a therapeutic elastic stocking (figure 2B) can be fitted up to the knee.

Figure 2. Adequate compression therapy. Photos of a patient's leg showing (A) a well-applied ambulatory compression bandage, and (B) a properly fitted graduated compression stocking.

Current status of guidelines

In the Netherlands it is advised to start compression therapy for all patients after an acute DVT. This is based on the multidisciplinary guideline "Diagnosis, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention Arterial Thrombosis" from 2009 and the NHG standard "Deep venous thrombosis and pulmonary embolism" from 2008, updated in 2015 and 2017 respectivly.[11,12] These guidelines recommend compression therapy with graduated compression stockings (class III, 34–46 mmHg) as soon as possible after diagnosing DVT, ideally for a duration of two years (level of evidence 1A according to the grading of the American College of Chest Physicians (ACCP)).[11,12] In cases of significant edema, treatment with a stocking can be preceded by a compressive bandage. The Dutch general practitioners guidelines (NHG standard) recommends that PTS can be diagnosed on clinical grounds without using any scoring system. The same guideline recommends that after one year compression therapy can be discontinued provided that there is no edema without compression therapy. The patient can continue to wear the compression therapy for symptom relief. In the

event of recurrent symptoms and/or edema, compression therapy can be used again. The focus on the NHG standard is rather on treatment of symptoms than on prevention of PTS. The English 'National Institute for Health and Care Excellence' (NICE) guideline from 2015 and the American College of Chest Physicians guideline from 2016 even recommend not routinely prescribing compression therapy.[13,14] Only in case of acute or chronic symptoms, compression therapy can be initiated. In this article we discuss on what grounds and on the basis of which studies the aim of prescribing compression therapy shifted towards treating symptoms rather than preventing PTS and discuss whether this is a justified approach.

Literature search

We systematically conducted a literature search in the PubMed, EMBASE.com and Cochrane Library databases. Search terms related to venous thrombosis were combined with terms for different types of compression therapies and limited to trials and reviews. The search was carried out on September 09, 2018 and yielded a total of 1390 articles of which 12 are suitable for this article (see figure 3)

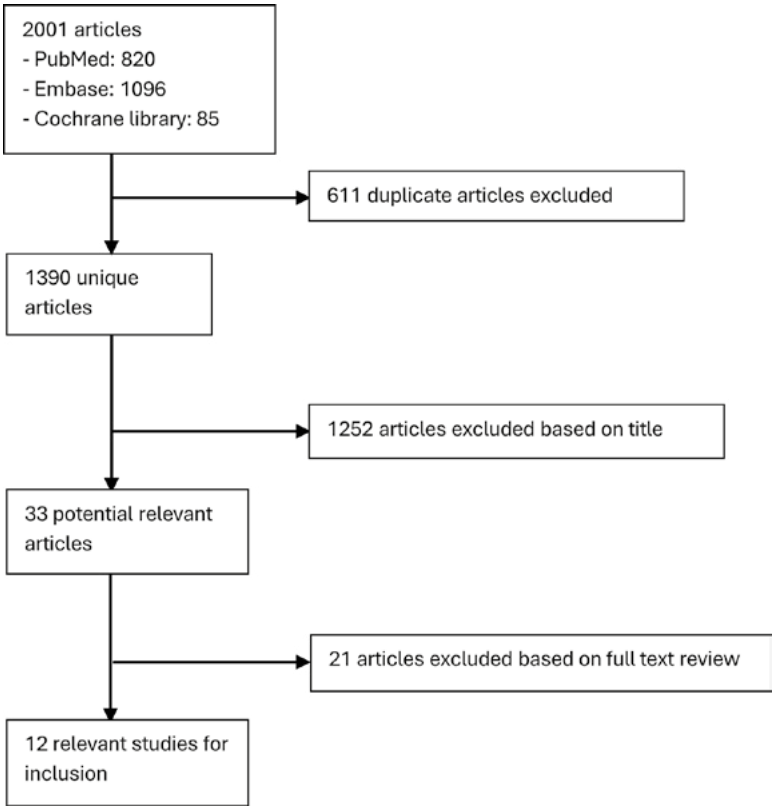


Figure 3. Flowchart of the systematic review

Effectiveness of compression therapy

In a Cochrane meta-analysis from 2017, the effectiveness of compression therapy in the prevention of PTS after DVT was studied in five RCTs with a total of 1393 patients.[15] The quality of the evidence was rated low due to heterogeneity between the studies and lack or an undefined degree of blinding. In three studies, compression stockings were compared with a control group without intervention.[16-18] Two studies compared GCS with placebo stockings.[19,20] In these five RCTs, with an average follow-up of two to six years, the use of GCS reduced the incidence of PTS after DVT with 38% (RR 0.62, 95% CI 0.38-1.01, p=0.05), but had no effect on the severity of PTS (RR 0.78, 95% CI 0.53-1.15, p=0.21). The SOX study by Kahn et al. was the largest study of those five RCTs. This study showed no difference between the cumulative incidence of PTS after two years in the GCS group (14%) versus the placebo group (13%, p=0.58).[20] However, compression therapy was started late (up to two weeks after DVT) and treatment adherence, defined as wearing GCS for at least three days a week, was only 56% after two years. These limitations may explain the failure to demonstrate the effectiveness of compression therapy in this study. However, based on this study, the NHG standard placed emphasis on treating complaints rather than on preventing PTS. The NICE and CHEST guidelines were also revised in 2015 after the publication of the SOX study.[13,14]

Duration of compression therapy

Three studies have investigated the optimal duration of compression therapy. The two largest studies are the OCTAVIA study and the IDEAL study in 518 and 865 patients respectively (figure 4).[1,21] In the OCTAVIA study, wearing GCS for one year after a proximal DVT was compared with two years of wearing GCS.[21] The incidence of PTS (one-time Villalta score ≥ 5) was 20% in the one year GCS group versus 13% in the two year GCS group (HR 1.60, 95% CI 1.02-2.50). Treatment adherence was high in this study (85.3% used GCS 6-7 days/week).

In the IDEAL study, patients after a proximal acute DVT were randomized between standard compression therapy for 24 months (n=428) or compression therapy with an individualized duration of at least six months and longer in the presence of PTS (n=432).[1] The primary endpoint was the cumulative incidence of PTS at two years, defined as a Villalta score ≥ 5 at two consecutive follow-up visits with an interval of at least three months.[6] In the intervention group, 55% of the participants (n=236) discontinued wearing GCS after 6 months and a further 11% (n=47) could stop wearing GCS after 12 months. The incidence of PTS after two years was 29% in the intervention group and 28% in the standard group (OR 1.06, 95% CI

0.78-1.44). When using the Villalta score ≥ 5 at only one follow-up visit, there was a statistical significant difference in the incidence of PTS in the intervention group (36%) compared to the standard group (22%) (RR1.6, 95% CI 1.2–2.3).[1] The average treatment adherence in the intervention group was 88% and in the standard group 71%. The quality of life (QOL) was similar in both groups. The individualized treatment turned out to be more cost-effective after two years.[22]

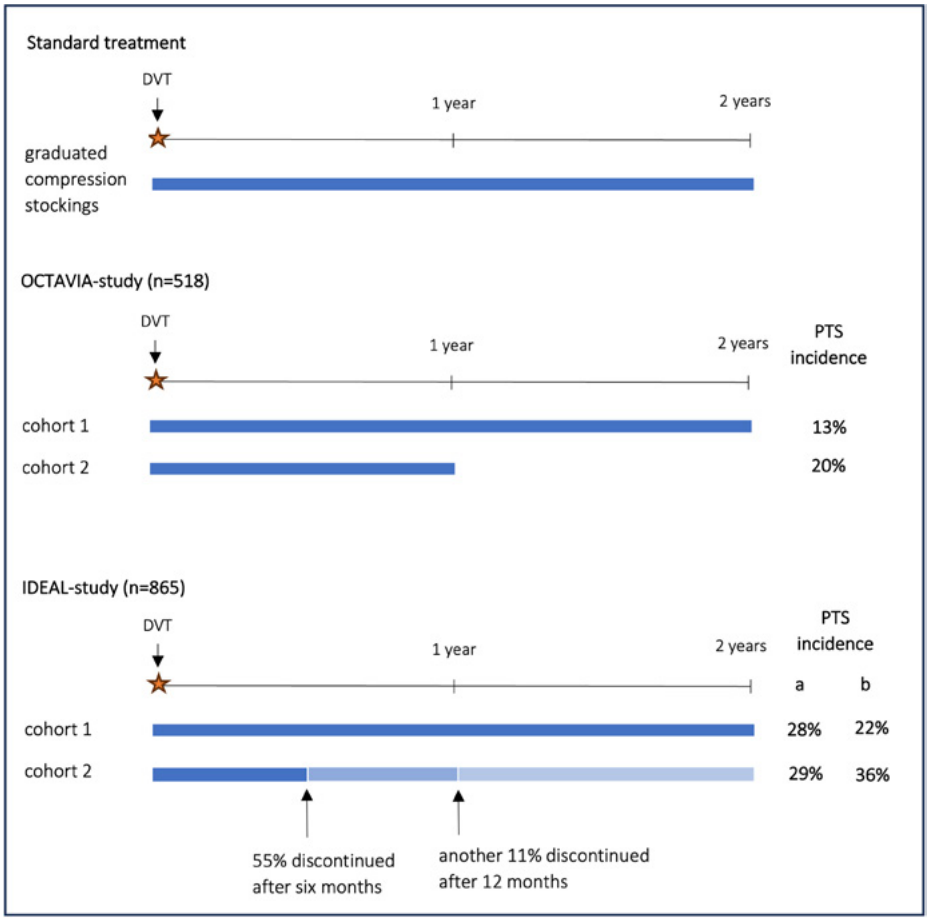


Figure 4. The two largest studies on the optimal duration of compression therapy. The blue bars indicate the duration of compression therapy in each treatment group of the trials. The incidence of PTS in the IDEAL study was highly dependent on how the outcome was measured: incidence was similar when the Villalta score was assessed twice (a), but differed significantly between treatment groups when it was assessed only once (b).

Based on the current literature, we recommend to prescribe compression therapy for preferably two years. The decision to shorten the duration of treatment should only be made by physicians who are skilled in recognising PTS, following a thorough venous history, focused physical examination, and an accurately assessed Villalta score. Discontinuing compression therapy after DVT based only on the history, without examining the legs, is not appropriate and will likely increase the incidence of PTS.

Acute compression after DVT

In a sub-study of the IDEAL trial, patients of nine centres (n=520) who received compression therapy after DVT within 24 hours of diagnosis were compared to patients of one centre (n=72) who received compression therapy after initial edema was resorbed.[23] Compression therapy in the acute phase of DVT resulted in an absolute reduction of the risk of ultrasound detected residual venous obstruction after an average of 5.3 months (46% versus 67%; OR 0.46; 95% CI 0.27-0.80). A significantly lower incidence of PTS was observed after 24 months in the patients in whom no residual obstruction was detected using ultrasound (46% versus 54%; OR 0.65; 95% CI 0.46-0.92). In a second sub-study of the IDEAL trial, 856 patients with acute DVT were randomized to compression therapy, consisting of bandaging or a graduated compression stocking suitable for the acute phase, versus no compression therapy.[24] This study showed that QOL during the acute phase and after three months did not differ between the two treatment groups. A lower Villalta score was measured in the compression group after three months, primarily due to less skin induration, hyperpigmentation, venectasia and pain on calf compression ($p<0.001$).

Side effects, treatment adherence and contraindications for compression therapy

The most commonly reported side effects of compression therapy are itching, discomfort, difficulty in applying compression, a warm sensation of the leg, skin irritation and cosmetic objections.[14] These complaints have also a direct influence on treatment adherence, one of the major problems in daily practice.[25] In the studies discussed in this article the treatment adherence varied from 55% to 92%, partly depending on the definition used. The most important contraindications consist of severe arterial insufficiency, neuropathy and heart failure.

Consideration and implications for clinical practice

Although most patients with PTS develop the disease within months after an acute DVT, it can occur even after two years after the DVT.[3] Venous leg ulcers also often develop after years which is considered as severe PTS. The recommendation

remains to prescribe compression therapy for a period of two years following DVT. Ideally, all patients should be actively monitored for signs of PTS for up to two years after DVT. Patients should not wear GCS on the day the Villalta score is assessed, as the presence of edema may not be optimally assessed. Furthermore, it is important to instruct patients when to make a follow-up appointment in case of specific signs of symptoms. Treatment adherence is another topic that should be discussed with all patients and ideally provide that all healthcare workers involved in the care of DVT or PTS patients are familiar with tools that can assist with wearing compression stockings. In addition, advise patients to avoid prolonged sitting or standing, to walk for at least half an hour every day, to elevate the affected leg during rest and to aim for a healthy weight.

Implication for further research

As the studies discussed show, the outcomes of a study depend on which definition of PTS is used. It remains uncertain whether the Villalta score is the most reliable clinical scoring system and how the optimal cut-off value for PTS could be determined. The Villalta score also does not include functional impairment, such as the pain free walking distance that might be a sign for the presence of venous claudication. Due to the lack of a gold standard, the sensitivity and specificity of the Villalta score can never be measured. Moreover, there is no consensus about the optimal time after DVT to establish PTS and whether multiple assessments are required for to determine the diagnosis. This highlights the importance of further validating the Villalta score in future research by assessing the correlation with residual venous obstruction and reflux on duplex ultrasound or with ambulatory venous pressure measurements. Although the Villalta score remains the best available assessment tool for diagnosing PTS, the limitations discussed should be taken into account when interpreting studies on PTS. Training in the use of the Villalta score is essential, both for recognising the clinical signs of early-stage PTS and for its application in research settings.

CONCLUSION

PTS is the most common complication of DVT. Without compression therapy about 50% of patients develop PTS following DVT, of whom 20% experience a severe form. Compression therapy significantly reduces the risk of developing PTS, especially when initiated directly after the diagnosis of DVT. The optimal duration of compression therapy has not been definitively determined. Based on current literature, our advice is to prescribe two years of compression therapy. The

decision to discontinue GCS treatment before two years should only be made by physicians who are skilled in recognising PTS following a thorough venous history, a focused physical examination and an adequately assessed Villalta score. Stopping compression therapy after DVT without looking at the legs based solely on the history is undesirable in our view and will increase the incidence of PTS. Patients should be instructed which symptoms warrant a follow-up appointment. Discuss treatment adherence with patients and provide lifestyle advice to reduce the risk of developing PTS.

REFERENCES

1. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, et al; IDEAL DVT investigators. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocationconcealed, non-inferiority trial. *Lancet Haematol*. 2018;5:e25-3.
2. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med*. 2004;164:17-26.
3. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res.* 2018;164:100-9.
4. Lubberts B, Paulino Pereira NR, Kabrhel C, Kuter DJ, DiGiovanni CW. What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis. *Thromb Haemost.* 2016;116:417-31.
5. Rabinovich A, Ducruet T, Kahn SR; SOX Trial investigators. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. *J Thromb Haemost.* 2018;16:262-70.
6. Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. *Haemostasis*. 1994;24:158a.
7. Wik HS, Enden TR, Ghanima W, Engeseth M, Kahn SR, Sandset PM. Diagnostic scales for the post-thrombotic syndrome. *Thromb Res*. 2018;164:110-5.
8. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost.* 2009;7:879-83.
9. Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidencebased consensus statement. *Phlebology*. 2018;33:163-84.
10. Partsch H. Compression therapy of the legs. *A review. J Dermatol Surg Oncol.* 1991;17:799-805.
11. Richtlijn 'Diagnostiek, preventie en behandeling van veneuze trombo-embolie en secundaire preventie arteriële trombose . Utrecht: Kwaliteitsinstituut voor de Gezondheidszorg CBO; 2008.
12. NHG-standaard 'Diepe veneuze trombose en longembolie' . Utrecht: NHG; 2017
13. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing . Londen: National Institute for Health and Care Excellence; 2016.
14. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315-52.
15. Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev*. 2017;9:CD004174.
16. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. *J Vasc Surg*. 2008;47:1015-21.
17. Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal vein thrombosis. *Lancet*. 1997;349:759-62.

18. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med.* 2004;141:249-56.

19. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. *Arch Intern Med.* 2001;161:2105-9.

20. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, et al; Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383:880-8.

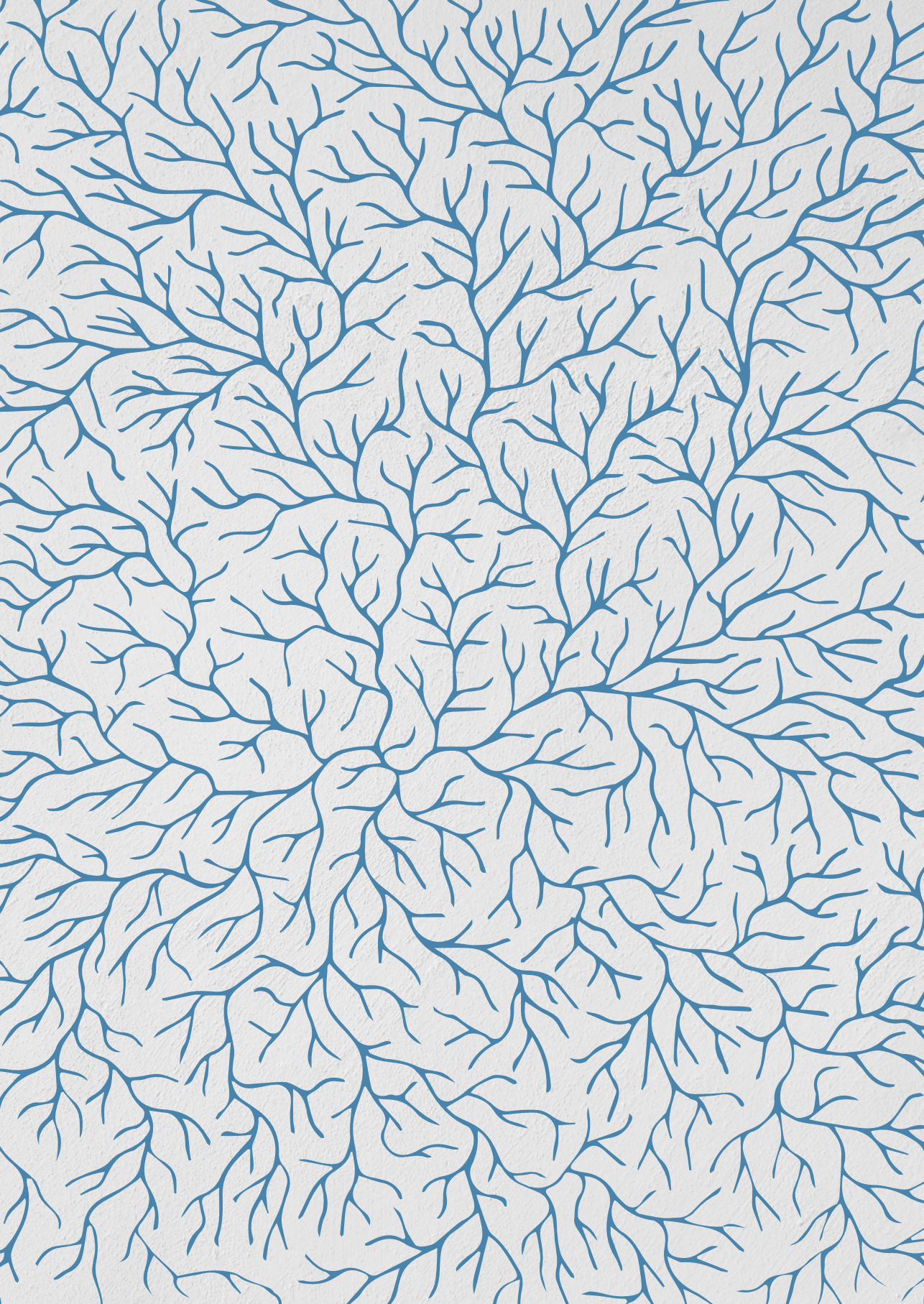
21. Mol GC, van de Ree MA, Klok FA, Tegelberg MJ, Sanders FB, Koppen S, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. *BMJ*. 2016;353:i2691.

22. Amin EE, Ten Cate-Hoek AJ, Bouman AC, Meijer K, Tick L, Middeldorp S, et al. Individually shortened duration versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome: a cost-effectiveness analysis. *Lancet Haematol.* 2018;5:e512-9.

23. Amin EE, Bistervels IM, Meijer K, Tick LW, Middeldorp S, Mostard G, et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. *Blood*. 2018;132:2298-2304.

24. Amin EE, Joore MA, Ten Cate H, Meijer K, Tick LW, Middeldorp S, et al. Clinical and economic impact of compression in the acute phase of deep vein thrombosis. *J Thromb Haemost.* 2018;16:1555-63.

25. Kankam HKN, Lim CS, Fiorentino F, Davies AH, Gohel MS. A summation analysis of compliance and complications of compression hosiery for patients with chronic venous disease or post-thrombotic syndrome. *Eur J Vasc Endovasc Surg.* 2018;55:406-16.



Chapter 6

Effect of exercise after a deep venous thrombosis: a systematic review

Bram Rook
Marie Josee E. van Rijn
Ilse E.P. Jansma
Catherine van Montfrans

A version of this chapter was previously published in: J Eur Acad Dermatol Venereol. 2024 Feb;38(2):289-301.

ABSTRACT

Post-thrombotic syndrome (PTS) is a common complication after deep vein thrombosis (DVT) and has a major impact on physical symptoms, quality of life (QOL) and economic costs. Relatively simple lifestyle interventions as physical exercise might reduce PTS severity and increase QOL. To evaluate the direct and long-term effects of physical activity in patients with an acute or previous DVT. We conducted a systematic review through an additional search from 2007 up to March 2022, to complement the comprehensive systematic review of Kahn et al. Articles evaluating the effect of exercise after DVT including symptoms, QOL and the incidence and severity of PTS, were included. Quality of the studies was assessed using a GRADE-like checklist and results were reported according to the PRISMA Statement. Ten studies were included, seven randomized controlled trials and three cohort studies. We identified three types of physical activity based on timing and duration; 1) early mobilisation in the acute phase of the DVT; 2) short duration exercise one year after DVT and 3) prolonged exercise during follow-up after a previous DVT. Early mobilisation showed improvement in QOL and pain reduction and after two years it resulted in a significant reduction of PTS severity. Prolonged supervised exercise resulted in improvement of QOL. In addition, positive effects on symptoms of venous insufficiency and muscle functions were observed. None of the included studies reported an increased risk of PTS or worsening of symptoms due to physical activity. Physical exercise after DVT is safe, improves QOL, reduces pain and decreases PTS severity. Lifestyle intervention such as guided individualised training programs can be a useful supplementary therapy for patients after DVT or for PTS patients. Optimal training programs may be identified by further studies that improve patient-oriented outcomes for both adults and children after DVT.

INTRODUCTION

Deep vein thrombosis (DVT) is a common condition, despite primary and secondary prevention, and may lead to the post-thrombotic syndrome (PTS). PTS can be described as a set of symptoms and signs of impaired venous outflow as a result of deep venous obstruction and/or reflux following DVT.[1,2] It occurs in 20-50% of DVT patients, of which 5-10% develops severe PTS, including venous leg ulcers (VLUs). PTS usually occurs in the first years after DVT, but may develop even after 10 to 20 years.[2,3] PTS patients not only have a lower quality of life (QOL) compared to DVT patients without PTS[2,4], they also impose a burden on the healthcare system due to high medical costs, lost workdays and loss of employment.[3] Different medical specialties such as general practitioners, dermatologists, phlebologists, angiologists and vascular surgeons encounter patients in different phases of the disease for treatment and interventions.

While DVT has to be prevented by all means, once it occurs, the risk or severity of PTS can be decreased by different types of therapy, including optimization of anticoagulant therapy, compression therapy, endovascular or surgical techniques to restore venous patency and lifestyle interventions such as weight loss and exercise.[3,5] Walking exercises improve ankle function and increase calve muscle pump (CMP) functionality, stimulating venous return.[6] On the other hand, impaired CMP functionality delays VLU healing and increases its recurrence.[7]

Unfortunately, there is a misconception among patients and physicians that exercise is harmful in the acute and chronic phase after DVT, while there is evidence to support the opposite.[8,9] A supervised exercise training program is recommended for PTS patients by the American Heart Association[3], based on the findings of the review of Kahn et al.[9] We aimed to further evaluate the direct and long-term effects of physical activity in patients with an acute or previous DVT including symptoms, QOL and the incidence and severity of PTS.

METHODS

Search strategy and data sources

A systematic search of PubMed and Embase was performed until March 14, 2022. Limits to publication date were applied from July 1, 2007 based on the inclusion period (until July 2007) of the systematic review of Kahn et al.[9] The main search terms comprised thromboembolism, physical activity and randomized controlled

trials (RCT) (supplementary table I for the complete search strategy). We included studies from this review according to our selection criteria as mentioned in the next paragraph. The current review was reported according to the guidelines for reporting systematic reviews in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline.[10]

Study selection and eligibility criteria

We included studies that investigated the effect of exercise or physical activity in DVT patients (with an acute or previous DVT) on the incidence of PTS, indicators of PTS and QOL. Studies preferably used a general accepted and predefined, well-described definition of PTS, such as the definition recommended by the 'International Society on Thrombosis and Haemostasis (ISTH)[1], or a commonly accepted instrument to assess venous symptoms of PTS that is regularly used in the literature such as the Venous Clinical Severity Scores (VCSS). Studies focussing on other outcomes related to PTS development or symptoms (e.g. leg flexibility, leg circumference, recanalization of the affected thrombotic veins) and/or QOL, were also included. Studies with more than 50% of the included patients having other causes of chronic venous insufficiency (CVI) than DVT, were excluded. Studies published in another language than English were excluded, as well as review articles. Kahn et al. conducted a complete and comprehensive review of the literature until July 2007.[9]

Screening

Two authors (BR and MR), independently screened the search results, following a pre-determined protocol. First, studies were screened by title. If it was clear from the title that the study was not relevant for our review, no further screening was done. If the title was potentially relevant or unclear, the abstract was read. After all potentially relevant studies were selected by title and abstract, they were checked on availability and whether they matched the eligibility criteria using the full text article. All full text articles were screened independently by two reviewers (BR and MR). In case of disagreement, a third reviewer (CvM) was consulted.

Data extraction

Characteristics of each included study were extracted using a standard form and included the number of patients, mean age, sex, length of follow up, type and duration of intervention, study population, study design and outcome tools used (presence and/or severity of DVT, presence and/or symptoms of PTS or PTS related outcomes, QOL). Data was adopted and used as published in the original article.

Different primary and secondary outcomes were used in the included studies. In supplementary table II, a list with the most important primary and secondary outcomes that were used is shown. In this table we describe the outcomes such as PTS, CVI and venous parameters along with their scoring methods. Moreover, questionnaires on QOL such as the VEINES-QOL or the SF-36 and on habitual exercise levels like the Godin Leisure Time Questionnaire are also shown and clarified.

Methodological quality assessment

Two authors (BR, MR) assessed the methodological quality of the included studies using a 13-item checklist with criteria based on a quality assessment instrument[18] and using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Studies received one point for each criterion that was met: 0-4 points was defined as a poor-quality study, 5-7 defined a fair quality study, 8-10 defined a good study and 11-13 defined a study of excellent quality. The items were classified into 4 factors: study aims and design, descriptions of treatment protocol, descriptions of methods, therapeutic/side effects and conduct of the study.

Summary measures

Variables are presented as mean or median with standard deviation (SD) or range if available, and dichotomous outcomes as percentages. Detailed explanations of results are presented in tables. P-values, odds ratio's and 95% confidence interval (CI) are presented if these statistics could be extracted from the original articles.

RESULTS

Study identification and selection

The search results are presented in a PRISMA flow diagram (figure 1). PubMed and the EMBASE database search resulted in 3154 publications. Search results were exported to EndNote and after eliminating duplicates and studies published before July 2007, 2506 publications were screened on title and, if necessary, on abstract, after which 100 studies remained. These studies were evaluated in more detail and 12 articles were left for full text review. Three studies met the eligibility criteria. Seven out of ten studies included in the systemic review of Kahn met our predefined eligibility criteria. Two studies focussing on pulmonary embolisms and one study investigating the effect of compression therapy during exercise therapy, were not included in our review. In total, ten studies were included in our systematic review for further analysis and assessment.[19-28]

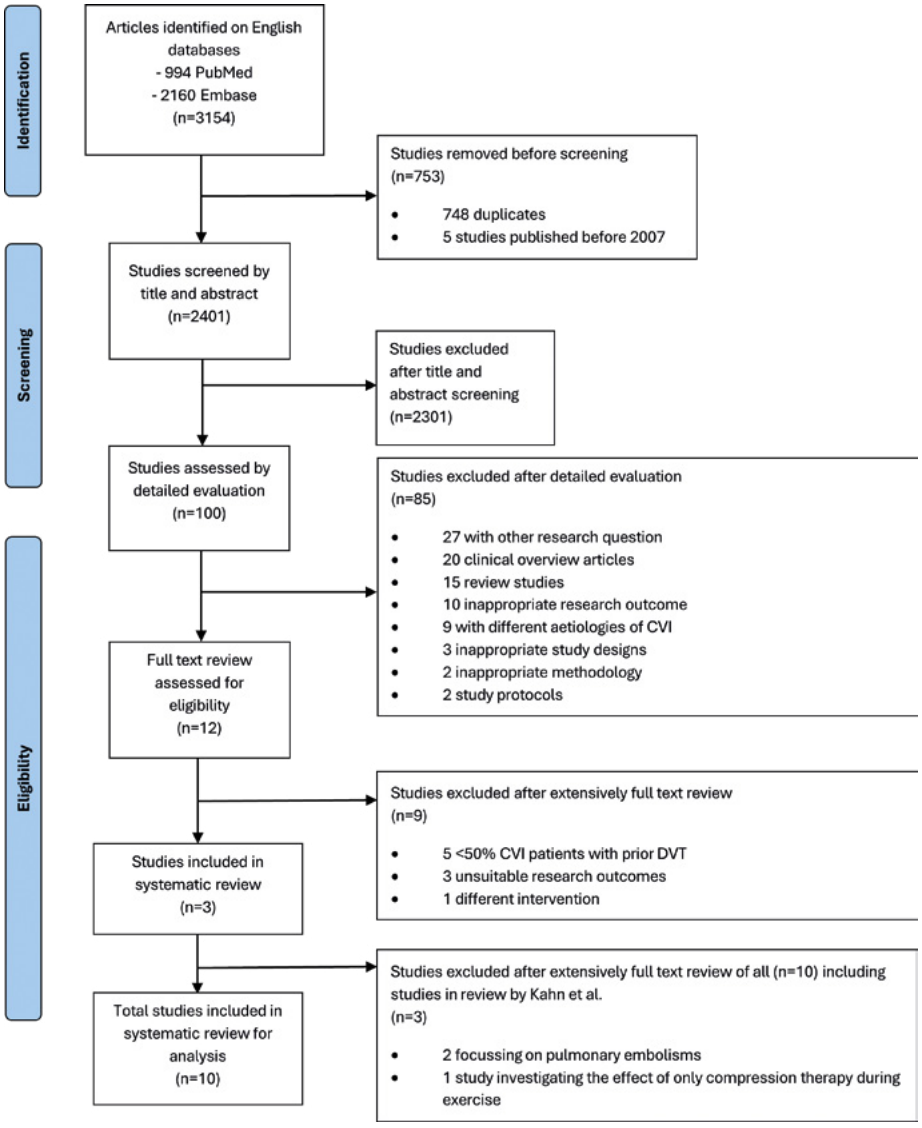


Figure 1. Flowchart of the systematic review. *CVI: chronic venous insufficiency; DVT: deep vein thrombosis*

Methodology quality assessment

Table 1 shows the results of the quality assessment. Supplementary table III provides a detailed overview of the conducted quality assessment, using a 13-item checklist.[18] One study was assessed as a study of excellent quality[27], five were rated as good quality studies[19, 23-26] and four studies were assessed as of fairly good quality.[20-22, 28]

Table 1. Results of quality assessment of included studies

Study	Poor quality (0-4)	Fairly good quality (5-7)	Good quality (8-10)	Excellent quality (11-13)
Junger, 2006 [19]			X (10 points)	
Blattler, 2003 [20]		X (7 points)		
Partsch, 2004 [21]		X (6 points)		
Kahn, 2003 [22]		X (7 points)		
Shrier, 2005 [23]			X (9 points)	
Shrier, 2009 [24]			X (10 points)	
Isma, 2007 [25]			X (9 points)	
Kahn, 2011 [26]			X (8 points)	
Padberg, 2004 [27]				X (11 points)
Hasan, 2020 [28]		X (7 points)		

Study designs

We included three cohort studies[22-24] and seven randomized controlled trails (RCTs).[19-21, 25-28]

Study characteristics

The characteristics of the studies are outlined in detail in table 2. All ten studies assessed the effect of physical exercise after DVT with different primary and secondary outcomes. Exercise was investigated as habitual physical exercise levels, short interventional exercises or individualised long-term exercise programmes. To assess how exercise could affect patients with a (previous) DVT, we present the results of studies that investigated the effect of 1) early mobilisation in the acute phase of the DVT; 2) short duration exercise one year after DVT and 3) prolonged exercise during follow-up after a previous DVT.

Study results

A summary of the results of the included studies is presented in table 3. Since the outcomes differed among included studies, we summarized the results of all ten studies individually. We ranked the studies in order of size according to the number of patients included or chronicity in case of follow-up studies.

Effect of early mobilisation in the acute phase of the DVT

A multicentre prospective study randomized 103 in-hospital patients, after a confirmed DVT, in an intervention group that could mobilise around the ward for at least five days and a control group that was prescribed strict bedrest.[19] Both groups were prescribed anticoagulation and compression stockings. The combined

primary outcome consisted of relevant pulmonary embolism (PE), diagnosis of PE, progression of thrombus, nosocomial infections, serious adverse events or death. Although not significant, less of the mobile patients reached the combined endpoint; 13.5% versus 28% bedrest patients (p=0.09), and the mobile patients less often had thrombus progression (7.7% versus 20%, p=0.09). There was no significant difference between the groups in change of VAS pain scores at 12 days of follow-up.

In another RCT, 53 patients were randomized to 1) keep bedrest for nine days, 2) perform walking exercises with therapeutic elastic stockings (TEK), or 3) perform walking exercises with compression bandages.[20] The QOL, the VAS pain score (in the compression bandage group) and reduction of edema was significantly higher at day nine in the groups that performed walking exercises. The relative risk of thrombus progression was lower in the exercise and compression groups ($p<0.01$).

Table 2. Study characteristics

Study	Study design	Study aim	Patient population + *inclusion criterium* - *exclusion criterium*	Intervention	Comparison	Main outcomes	Follow-up
Junger, 2006 [19]	Multicentre prospective RCT	To study the effect of mobilization directly after DVT	+ presence of a proximal DVT diagnosed with duplex sonography or phlebography + in-patients and admitted for DVT, at least six days hospitalized + Anticoagulation and compression therapy similar in both groups - lysis therapy/ thrombectomy - concurrent symptomatic PE	Instruction to mobilise on the ward for at least five out of six days after DVT diagnosis	Strict bedrest for at least five out of six days	- Combined primary endpoint (clinically relevant PE, diagnosis of PE, progression of thrombus, nosocomial infection, serious adverse events, death) on final examination on day 10-12. - Occurrence of single events of primary endpoint - Degree of leg pain (VAS scale, 0-100)	12 days
Blattler, 2003 [20]	Single centre RCT	To study the effect of immediate compression therapy and ambulation on PTS development	+ Mobile patients with DVT + Symptoms <14 days - Therapy already started - thrombolysis/ thrombectomy indicated	I: inelastic compression therapy and walking for nine days II: elastic compression therapy and walking for nine days	III: Bed rest up to nine days without compression therapy	- Pain scores at nine days - Leg circumference - DVT related QOL - Recanalization	nine days
Partsch, 2004 [21]	Single centre RCT (same cohort as Blattler et al. [21])	To study the effect of immediate compression therapy and ambulation on PTS development	+ Mobile patients with DVT + Symptoms <14 days - Therapy already started - thrombolysis/ thrombectomy indicated	I: inelastic compression therapy and walking for nine days II: elastic compression therapy and walking for nine days	III: Bed rest up to nine days without compression therapy	- PTS severity (Villalta score) at two years - Pain scores - Leg circumference - Recanalization	two years

Table 2. Continued

Study	Study design	Study aim	Patient population + *inclusion criterium* - *exclusion criterium*	Intervention	Comparison	Main outcomes	Follow-up
Kahn, 2003 [22]	Single-centre prospective cohort study	To study the effect of exercise on venous symptoms and the effect of PTS on exercise	+ Subjects with a first episode of unilateral DVT at least one year earlier - Symptomatic pulmonary embolism - Unable to do treadmill exercises	Treadmill walking or running that caused sweating and mild tachypnea for max. 30 min	- Comparison of post and pre-exercise symptoms - Comparison affected and non-affected leg - Comparison between patients with and without PTS	- Severity of individually venous symptoms after 30 minutes - Ligament flexibility - Muscle fatigability - Leg volume	30 minutes
Shrier, 2005 [23]	Multicentre prospective cohort study	To study the effect of physical activity one month after DVT on PTS severity and activity four months later	+ New diagnosis of DVT, confirmed with duplex ultrasound or contrast venogram - Unable to adhere to the study protocol - Expected life span < one year	N/A	N/A	- Δ PTS severity between one and four months visit (Δ Villalta score >0) - Change in self-reported physical activity level (Godin Questionnaire)	four months
Shrier, 2009 [24]	Multicentre prospective cohort study (same cohort as Shrier et al. [26]) Single centre RCT	To study the effect of physical activity one month after DVT on PTS severity and activity two years later	+ New diagnosis of DVT, confirmed with venous duplex ultrasound or contrast venogram - Unable to adhere to the study protocol - Expected life span < 1 year	N/A	N/A	- Development of PTS (Villalta score) over two-year period. - Self-reported physical activity leveln (Godin Questionnaire)	24 months

Table 2. Continued

Study	Study design	Study aim	Patient population *+ inclusion criterium* *- exclusion criterium*	Intervention	Comparison	Main outcomes	Follow-up
Isma, 2007[25]	Single centre RCT	To study the effect of supervised exercise on recanalization after DVT by phlebography, QOL and leg circumference	+ New diagnosis of DVT with phlebography. - Other disease or earlier thrombosis - Age > 75 yrs - DVT diagnosed only by ultrasonography - Inadequate phlebography for severity-scoring of the thrombosis	Six months of daily walking exercise and weekly supervised exercise	Standard DVT treatment only	- Recanalization on phlebography at six months - Quality of life - Calf circumference	six months
Kahn, 2011 [26]	Two-centres RCT	To study the effect of exercise training after DVT on QOL and PTS severity	+ Unilateral symptomatic DVT + Diagnosis > six months + Presence of PTS - Contra-indication for exercise training - Expected life span < six months - Pregnant or lactating - Open venous leg ulcer - Unable to visit check-ups	Six-month supervised and individualized exercise training program designed to improve cardiovascular fitness and leg strength and flexibility.	One-hour education session on PTS with monthly phone follow-ups to simulate attention and contact received by the intervention group. Patients were asked to not alter their habitual activity level.	- Venous disease-specific quality of life at six months - Severity of PTS (Villalta score) - Physical component of functional health and well-being (SF-36 PCS) - Leg strength - Quadriceps flexibility	six months

Table 2. Continued

Study	Study design	Study aim	Patient population + *inclusion criterium* - *exclusion criterium*	Intervention	Comparison	Main outcomes	Follow-up
Padberg, 2004 [27]	Single centre RCT	To study the effect of a supervised exercise program on calf muscle strength and haemodynamics	+ Patients with advanced CVI (CEAP 4-6) + CVI evidence with duplex ultrasound or APG - Painful or excessive (>4cm) ulceration - Recognised non-compliance - Absence of an objective evidence of a venous cause - Recent acute thrombosis - ABI < 0.9	Three months of structured supervised exercise program followed by three months of unsupervised exercise and compression stockings	No additional exercise with compression stockings	- Calf pump function - Calf muscle strength - VCSS - Quality of life	six months
Hasan, 2020 [28]	Pilot RCT	To study the eligibility of and compliance to exercise therapy in children and adolescents as well as the PTS incidence and QOL in this group.	+ outpatient subjects between 7-21yrs of age with a new, first lower extremity DVT - Unable to exercise - Contra-indications to increasing activity that could impair existing medical conditions.	Sixteen-week period with eight weeks of individualized physical aerobic activity and education on benefits of physical activity initiated three months post DVT	Habitual activity after education on benefits of physical activity and encouragement to exercise	- feasibility outcomes: eligibility, consent, compliance and trial completion - Changes in PTS (Manco-Johnson Instrument) - Changes in QOL	nine months

DVT: Deep vein thrombosis; QOL: Quality of life; VAS: visual analogue scale; NS: not significant; IQR: inter quartal rage; PTS: post-thrombotic syndrome; SD: standard deviation; OR: odds ratio; CI: confidence interval; EF: ejection fraction; RVF: residual volume fraction; SEM: standard error of the mean; VCSS: Venous Clinical Severity Score)

The long-term follow-up was reported of these patients.[21] The two groups that immediately mobilized were combined and all patients were allowed to mobilise after nine days and were stimulated to wear compression stockings for the next two years. Follow up visits were performed in 70% of the patients. A significant lower median (inter quartile range (IQR)) Villalta score was found in the two combined walking exercise groups (5 [3-6.5]) compared to the bedrest group (8 [6.5-11], p<0.01), despite a lower adherence to compression therapy for more than one year (50%) in the walking group compared with the bedrest group (73%). The incidence of PTS was lower in the exercise group (54%) compared with the bedrest patients (82%), although this was not statistically significant. No differences between the groups were found for pain scores, leg circumference and thrombus regression.

Effect of short duration exercise after DVT

The single study included is a cohort study that analysed the effects of 30 minutes treadmill exercise in 41 patients with DVT one year earlier[22], of which 19 (46.3%) had PTS and 22 (53.7%) did not. To examine whether the presence of PTS limited the ability to exercise, the primary outcome included VAS scores and muscle functions. No difference at baseline between patients was found in habitual activity levels using the Godin questionnaire. Severity of symptoms did not differ between the affected and unaffected leg after exercise and this was not influenced by the presence or severity of PTS. In PTS patients, there was a significant increase in muscle flexibility in the affected leg for the gastrocnemius muscle (4.5°, p=0.003) and the soleus muscle (5.7°, p=0.001) after treadmill exercise. Leg volume in PTS patients increased significantly more in their affected leg versus their unaffected leg (mean between leg difference +53 ± 108 mL), compared with patients without PTS (mean between-leg difference -15 ± 64 mL, p=0.018). The increase was most prominent in severe PTS.

Table 3. Patient characteristics, main results and conclusion per study

Study	Characteristics	Outcomes	Conclusions
1. Effect of early mobilisation in the acute phase of the DVT			
Junger, 2006 [19]	N=103 52=mobile 51=immobile Mean age: 60yrs Male 56%	Occurrence of primary outcome (combined events), n (%) Mobile group: 7 (13.5%) vs. immobile group: 14 (28%) p=0.088 (95%CI:–0.301-0.010) Number of thrombus progression or new thrombus events, n (%) Mobile group: 4 (7.7%), vs. immobile group: 10 (20%) p=0.088, *95%CI not mentioned* Number of clinically relevant/symptomatic PE events, n (%). Mobile group: 1 (1.9%) vs. immoblie group: 5 (10%) p=0.109, *95%CI not mentioned* Number of deaths, n (%) Mobile group: 0 (0%) vs. immobile group: 0 (0%) Mean (±SD) VAS scores (0-100) for leg pain from day one vs. final examination (day 10–12).* Mobile group: 54.1 (±30.4) vs. 20.7 (±19.2) Immobile group: 41.0 (±26.8) vs. 14.0 (±11.1) * *intention-to-treat analysis*	A trend was found in favor of mobilization with less events, especially number of thrombus progresson and relevent PE, although not significant No significant difference in pain reduction
Blattler, 2003 [20]	N=53 17=bedrest 18=stockings and mobilisation* 18=bandage and mobilisation* * *stockings+ bandage = compression group* Mean age: unknown Male: unknown	Pain scores (VAS scale)* Mobile + only bandage vs. bed rest p<0.05‡ Edema (difference of mean lower leg circumference)* Mobile + compression group vs. bedrest p<0.001¶ DVT related QOL* Mobile + compression group vs. bed rest p<0.05¶ Relative risk (95%CI) on thrombus progression Mobile + compression group 6/27 22% vs. bedrest 4/10 40% RR 0.56; 95%CI 0.20-1.57; NS * *no exact numbers provided, data presented in figures in article.*	The combination of mobilisation and compression therapy directly after DVT diagnosis reduced pain and edema and improved QOL at nine days

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
Partsch, 2004 [21]	N=37 of 53 left after two years FU 11=bedrest 13=stockings and mobilisation 13=bandage and mobilisation Mean age: 56yrs Male: 62.0%	Median (IQR) PTS severity (Villalta score) after two years Mobile: 5 [3-6.5] vs. bedrest: 8 [6.5-11] P<0.01 Incidence of PTS development (Villalta ≥ 5) after two years Mobile: 14/26 (54%) vs. bedrest: 9/11 (82%) RR 0.66; 95%CI 0.42, 1.03; NS Median (IQR) difference of pain (VAS scale) after two years Bedrest: 15 (8.5-35) vs. stockings and mobile: 20 (7-23.5) vs. bandage and mobile 17 (7-26.5) NS Median (IQR) difference of pain by Lowenberg test (mmHg) after two years Bedrest: 20 (0-15) vs. stockings and mobile: 0 (-10-30) vs. bandage and mobile 0 (-17.5-40) NS Median (IQR) difference of calf circumference (cm) between DVT leg and contralateral leg after two years. Bedrest: 1.5cm (0.5-1.75) vs. stockings and mobile: 0.5cm (-1- 1.5) vs. bandage and mobile: 1.0cm (-0.25-2) NS Percentage of recanaliation, progression or regressoin of the primary extension of DVT after two years Mobile group: no thrombi 58.3%, unchanged 33.3%, progress 8.3% Bed rest group: no thrombi 54.5%, unchanged 36.4%, progress 9.1% NS	The combination of mobilisation and compression therapy directly after DVT diagnosis decreased severity of PTS at two years.

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
2. Effect of short duration exercise after DVT			
Kahn, 2003 [22]	N=41 (19 with PTS) Mean age: 51yrs Male = 57.8%	Difference before - after exercise in symptom rating in cm on a VAS scale, all patients Affected leg: ranged -0.01 to +0.52, NS Unaffected leg: ranged -0.04 to +0.44, NS *Outcomes were not influenced by presence or severity of PTS* Mean difference from pre-exercise after exercise of leg volume (mL±SD), all patients Affected leg: +76 mL±110, p<0.001 unaffected leg: +59 mL±82, p<0.001 Mean difference in leg volume (mL±SD) after exercise, affected leg vs unaffected leg, only PTS patients Affected leg +53±108ml vs. unaffected leg -15±64mL, p=0.018 *More severe PTS gained more volume in the affected leg* Mean difference in muscle flexibility after exercise between affected leg and unaffected leg in PTS patients vs. non-PTS patients. Gastrocnemius flexibility: +4.5°, p=0.0029 Soleus flexibility: +5.7°, p=0.0011 No correlation between change in leg volume and change in muscle flexibility was found for gastrocnemius muscle R^2=*0.03* or soleus muscle R^2=0.07).	Treatmill exercises did not worsen symptoms in patients with or without PTS in their affected leg compared to their unaffected leg Exercise led to a greater mean leg volume in patients with PTS in their affected leg compared to their unaffected leg In PTS patients exercise led to a greater increase in muscle flexibility between the affected and unaffected leg compared to non-PTS patients
3. Effect of prolonged physical exercise after DVT			
Shrier, 2005 [23]	N=301 Mean age: 55yrs Male: 50%	Adjusted OR[¥] for worsening of PTS (ΔVillalta score >1) after four months (95%CI) according to activity level at one month*: No physical activity: OR = 1.0 (reference) Mild-moderate active group: OR = 0.93 (0.47-1.87) Highly active group: OR = 0.52 (0.23-1.15) * *When worsening was recalculated as ΔPTS > 0 as compared with > 1, the results were similar but the evidence for a gradient effect was stronger: OR mildly to moderately active = 0.76 (0.40, 1.44), and OR highly active = 0.52 (0.26, 1.03).* Change in physical activity level at four months among active patients (Godin score at one month > 0 (n=220)) 42.3% (n=93) reached the same phyical activity level 13.2% (n=29) had increased physical activity levels 44.5%% (n=98) had decreased physical activity levels* * exercise-induced leg symptoms were reported as the cause in 25% (n=55) of all previously active patients.	An increase in habitual physical activity one month after DVT did not worsen PTS at four months Nearly half of all previously active subjects had a decrease in physical activity level, with exercise-induced leg symptoms being the cause in 25% of all former active patients

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
Shrier, 2009 [24]	N=387 Mean age: 58yrs Male: 50.5%	Adjusted OR† for developing PTS within two years after DVT (95%CI)* Mild to moderate activity levels within one month after diagnosis: 1.64 (0.85-3.15) High levels of activity within one month after diagnosis: 1.33 (0.68-2.06) ** data of patients with 'no activity' not provided* Association between occurrence of PTS and physical activity level at two years follow-up§, proportion, % (95%CI)* No activity (Godin=0 at 2 years): None to mild PTS 19.6 (13.6-25.6) Moderate to severe PTS 42.4 (29.2-55.7) Mild to moderate activity level (Godin=1-20 at 2 years): None to mild PTS 24.9 (19.0-30.9) Moderate to severe PTS 20.6 (10.5-30.8) High acitivity level (Godin >20 at 2 years): None to mild PTS 55.5 (48.8-62.2) Moderate to severe PTS 36.9 (24.0-49.8) ** Overall dfference of physical activity between none to mild vs moderate to severe PTS was statistical significant, p=0.002.*	The level of exercise in the first month after DVT was not associated with the two-year risk of developing PTS Patients with PTS had lower activity level than patients without PTS. This was more prominent with increasing PTS severity
Isma, 2007 [25]	N=72 Mean age: 54yrs Male: 52%	Median calf circumference of affected leg (cm (range)) at six months follow-up Exercise group 38cm (25.5-48) vs. control group 36cm (32.5-44) NS Median QOL (VAS score 0-100mm (range)) at six month follow-up Exercise group 4(0-74) vs. control group 7.5 (0-95) NS Mean phlebographic DVT score (Björgel score (SD)) after six month follow-up Exercise group 3.0 (4.9) vs control group 1.1 (2.8) NS	No difference in calf circumference, QOL or phlebographic score was seen after daily exercise training for six months

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
Kahn, 2011 [26]	N=43 Mean age: 46yrs Male: 44.4%	Mean difference of VEINES-QOL (SD) from baseline to six months Exercise group 6.0 (5.1) vs. control group 1.4 (7.2) Between group difference 4.6 points (95%CI: 0.54-8.7) p=0.027 Mean difference of PTS severity from baseline to six months; Villalta score (SD) Exercise group -3.6 (3.7) vs. control group -1.6 (4.3) Between group difference -2.0 points (95%CI: -4.6-0.6) p=0.14 Mean difference on SF-36 PCS scale (SD) from baseline to six months Exercise group 5.6 (7.7) vs. control group 0.2 (7.6) Between group difference: 5.4 points (95% CI: 0.5-10.4) p=0.03 Mean difference of leg strength from baseline to six months; number of heel lifts (SD) Exercise group 5.2 (10.6) vs. control group -2.5 (10.8) Between group difference: 7.7 (95% CI: 0.7-14.7) p=0.03 Mean difference of quadriceps flexibility from baseline to six months; degrees (SD) Exercise group 10.2 (20.5) vs. control group 0.3 (6.6) Between group difference: 9.9 (95% CI: -1.0-20.7) p=0.04	Six-month exercise training improved the disease specific QOL, leg strength, quadriceps flexibilty and the physical component of health related QOL, but not Villalta score

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
Padberg, 2004 [27]	N=30 (50% with prior DVT) Mean age: 70yrs Male: 100%	Mean difference in calf pump functions from baseline to six months (% (±SEM)) Ejection fraction (EF): Intervention group 3.5±2.7 vs. control group -1.4±2.1 P=0.03 Residual volume fraction (RVF): Intervention group -8.8±4.6 vs control group 3.4±2.9 p=0.03 Mean difference in muscle strenght (peak torque/body weight) at slow speed from baseline to six months (number (±SEM)) Intervention group 3.1±1.4 vs. control group -1.0±1.1 p=0.05 Mean difference in muscle strenght (peak torque/body weight) at fast speed from baseline to six months (number (±SEM)) Intervention group 2.8±0.9 vs. control group -0.3±0.6 p=0.03 Mean difference of VCSS score from baseline to six month (total (±SEM)) Intervention group -0.3±0.9 vs. control group 0.1±1.0 p=0.51 No difference in QOL between both groups (data not shown).	After exercise training, the EF increased significanly and the RV decreased significantly Both slow and fast peak torque, to measure calf muscle strength, improved in the affected legs of patients receiving exercise regimen The exercise program did not lead to any differences in venous severity score or QOL

Table 3. Continued

Study	Characteristics	Outcomes	Conclusions
Hasan, 2020 [28]	N=23 Mean age: 15yrs Male: 48%	Adherence to the allocated intervention and overall activity Only three of the 11 patients adhered to prescribed activity during active study phase. No differences in self-reported physical activity scores between groups during entire trial. In postintervention phase, only 20% of all patients maintained target activity levels. Mean change of PTS score from baseline to six months of follow-up (mean Manco-Johnson Instrument score (SD)) Intervention 0.0 (0.50) vs. control group +1.3 (0.8). p=0.0017 Mean change of total QOL score from baseline to 6 months of follow-up (mean QOL score (SD)) Intervention +5.5 (14.3) vs. control group +24.5 (14.2) p=0.023 Elastic compression stocking use at six-month follow-up Intervention group 44% vs control group 85%	Enrollment and randomization of pediatric DVT patients of prescribed exercise therapy was feasible, however adherence and retention was low Activity lowered PTS score The control group had a statistical significant better mean QOL score than the intervention group although both showed a substantial increase in QOL scores

DVT: Deep vein thrombosis; QOL: Quality of life; VAS: visual analogue scale; NS: not significant; IQR: inter quartal rage; PTS: post-thrombotic syndrome; SD: standard deviation; OR: odds ratio; CI: confidence interval; SEM: standard error of the mean; VCSS: Venous Clinical Severity Score)† Adjusted for age, sex, body mass index (BMI) and pre-DVT physical activity level (baseline Godin score) and disease severity at one month; ¶ In favour of the mobile and compression (combined) group; ‡ In favour of the mobile and bandage (combined) group; § Scored on the Godin questionnaire (21); ¥ Adjusted for age, sex, pre-DVT physical activity level and venous disease-specific QOL at one month.

Effect of prolonged physical exercise after DVT

First, a cohort study of 301 patients evaluated whether the level of self-reported physical activity at one month after an acute DVT led to worsening of PTS severity at four months of diagnosis, defined by an increase of the Villalta score.[23] Three groups, 1) inactive (Godin score 0, n=99), 2) mild to moderate active (0-20, n=97) and 3) highly active (>20, n=102) were identified at one month after DVT. At four months follow-up no positive or negative effect on PTS severity was shown. Former active patients (Godin > 0 pre DVT (n=220)) had self-reported activity levels at four months after DVT diagnosis that were either similar (42.3%, n=93) or showed an increase (13.2%, n=29), meaning that 44.5% (n=98) had a decreased activity level at four months. Fifty-five of those 98 patients stated that the decrease of their activity levels was due to exercise-induced leg symptoms, while the rest had reasons unrelated to their DVT.

The same research group investigated if the self-reported physical activity levels were associated with the risk of PTS occurrence at any moment within the first two years after DVT using the Villalta score[24] for 387 patients, an extended patient cohort of their prior study. Physical activity at one month after the DVT was not significantly associated with an increased risk of PTS occurrence in the next two years. Comparable results were shown after adjusting for potential confounders such as PTS severity, age, sex, BMI, pre-DVT physical activity level and disease-specific QOL scores. At two years follow-up, patients who had developed PTS were less physically active. This decrease in physical activity was greater among moderate and severe PTS patients than in patients with mild PTS (p=0.002).

Another RCT randomized 72 patients to investigate the effect of supervised physical exercise on venous symptoms and recanalization of the prior thrombosed vein after a first episode of acute DVT.[25] All patients received anticoagulation therapy and TEK whereas the intervention group (n=32) in addition performed daily walking exercises and weekly supervised exercises for six months. Of the total of 67 (93%) patients who completed follow-up, the Björgell phlebographic score showed no statistically significant difference at six months between the intervention group 3.0 (SD 4.9) and the control group 1.1 (SD 2.8). Overall, QOL on a VAS scale of 0-100 improved and calf circumference in cm was reduced in both groups without any significant difference between the groups. There were no reports of recurrent DVT, PE or other complications.

In an RCT studying the effect of a six-month supervised exercise training program to improve leg strength, leg flexibility and overall cardiovascular fitness,

43 patients diagnosed with PTS at least six months after DVT were randomized into an intervention group (n=21) and a control group (n=22).[26] A significant between-group difference in disease-specific QOL, using the VEINES-QOL questionnaire, was shown in favour of exercise of 4.6 points (95%CI: 0.54-8.7, p=0.03). A difference of three points was considered clinically relevant. The effect of exercise on severity of PTS was not significantly different between the exercise group and the control group. However, the physical component score on the SF-36, leg strength and quadriceps flexibility were all statistically significant in favour of the exercise group.

Next, 30 male veterans with CVI, 50% of whom had a history of DVT, were included in a RCT to compare the effect of a structured exercise program, consisting of individualized physical training sessions versus TEK only.[27] The 17 patients in the intervention group followed weekly training sessions for three months, after which they were encouraged to continue for another three months. Of the 28 (93%) patients who completed follow-up, there was a significant difference in venous ejection fraction (p=0.03), residual volume fraction (p=0.03) and measurements of the isokinetic peak torque per body weight, used to test muscle strength of different angular velocities at both slow (p=0.05) and fast speed (p=0.03), all in favour of the exercise group. No effect was found on CVI severity, functional mobility or QOL.

To investigate the feasibility of an individualised exercise program for paediatric and adolescent patients after an acute DVT, 23 patients (age 7-21 years) were randomized into two groups at three months after diagnosis.[28] Both groups were educated on the positive effects of physical exercise and were stimulated to exercise. The intervention group was also stimulated to increase activity level by 25% for eight weeks to each individual's target level based on their baseline activity level of the previous four weeks tracked by a Fitbit tracking device. After the eight-week 'active' period patients could choose to maintain their increased exercise levels or return to their baseline levels. Besides feasibility, change in PTS score, assessed by the Manco-Johnson Instrument, was measured. A higher score indicates worse PTS severity. In total 15 of 23 patients completed the trial, and only three of 11 patients in the intervention group followed the eight-weeks prescribed regimen. During the trial self-reported physical activity did not differ between the groups, although the mean change (SD) in PTS scores at six months follow-up in the intervention group was 0.0 (SD=0.50) versus an increase of 1.3 (SD=0.8) in the control group (P<0.05).

DISCUSSION

In this review of ten studies focussing on physical exercise after DVT, we found that the relatively 'simple' intervention of exercise had positive effects on both short and long term outcomes. Short term outcomes after early mobilization in the acute phase of the DVT included a reduction in PTS severity, an increase in QOL and a reduction of pain and edema. Long term outcomes after exercise training in the chronic phase after DVT continued to improve QOL as several secondary outcomes associated with severity of PTS such as improved venous haemodynamics and enhanced muscle strength and muscle flexibility. Interestingly, higher levels of physical activity did not result in an increase of PTS severity. Patients with PTS tend to have a lower activity level than patients without PTS, which is more prominent with increasing PTS severity. In paediatric and adolescent patients adherence to a supervised physical exercise program proved to be difficult for this younger patient group.

Based on their systematic review of 2008 Kahn et al.[9] already promoted a positive role for exercise in patients with an acute or previous DVT without worsening of PTS symptoms. Our review supports these conclusions. Moreover, both Kahn et al. in their review and others also studied the incidence of complications like PE or recurrent venous thrombotic events (VTE), which did increase with increased physical exercise.[2,5] The additional studies we included in this review did not describe these possible side effects. The positive effect of exercise on QOL was found both for exercise in the acute phase of DVT, as well as in patients that had already developed PTS. The RCT performed by Kahn in 2011 confirmed the conclusions from their 2008 review and showed that a supervised six-month exercise training program in PTS patients improved QOL, leg strength and quadriceps flexibility, the latter being associated with improvement of venous return.[6]

Schrier et al. demonstrated that nearly half of the previously active patients had a reduction in physical activity level after DVT and patients appeared to be less active with increasing PTS severity.[24] This might be out of fear for worsening of symptoms or to avoid pain, which both are known to predict low physical activity in leg ulcer patients.[29] Twenty-five percent of patients in the cohort study of Shrier with reduction of their physical activity levels after DVT diagnosis stated that exercise-induced leg symptoms were responsible for this reduction. A session of treadmill exercises in another study showed no worsening of symptoms in the patient's affected leg compared to the unaffected leg. Worsening or development of PTS after longer follow-up was not shown in any study in our review. Thus, the

specific cause of being less active after DVT, or in case of PTS, is unclear and should be further elucidated in future studies, along with the role of physicians, trainers and supervisors could play.

In most trials, both PTS occurrence and severity was scored using the Villalta scale. Though recommended by the ISTH, this is a subjective scale and might have been interpreted differently by different assessors.[1] Moreover, this scoring modality does not cover all important aspects of PTS, such as venous claudication. Many studies investigated however more important variables, such as venous hemodynamic parameters and symptoms apart from the Villalta score. Many studies did emphasise the importance of QOL, which is an increasingly important outcome in chronic diseases as PTS. Since PTS imposes a great burden on patients' QOL, the improvement of QOL due to exercise which was found in several trials, is promising.

PTS not only reduces QOL, it also impose a burden on the healthcare system with significant financial consequences, especially in case of VLUs.[3,4] The consumption of care from both in-hospital and home care organisations increases medical costs and the combination of direct and indirect societal costs leads to considerable economic burden.[30] The positive outcomes in this review can be of great importance to potentially reducing these costs. Several studies have found a long-term positive effect of physical exercise on preventing worsening of PTS, venous symptoms and QOL. That exercise therapy can have a long-lasting effect suggests that this could be an inexpensive tool to reduce those costs, although this should be the focus of further research.[3]

In paediatric patients leg discomfort and a lack of motivation and time appeared to be reasons for their inability to adhere to prescribed exercise schedules. Since this was a pilot study with few patients primarily focussing on the feasibility of physical exercise programs in paediatric patients, the results of the PTS and QOL scores must be interpreted with caution. Moreover, this study showed the difficulty for younger patients to adhere to a physical activity program. More knowledge on how to motivate paediatric patients after DVT to exercise is necessary to overcome these concerns.

The limitations of this review are due to the heterogeneity in methods and outcomes of the included studies and therefore a meta-analysis could not be performed. For example, instead of using the Villalta score for PTS as primary outcome, a significant number of trials investigated surrogate endpoints, like leg or joint flexibility, leg circumference or recanalization of the affected vein. These outcomes can be

associated with venous disease severity[6], but do not automatically imply the presence of PTS or indicate the severity of PTS. In some studies, no associations were found between physical exercise and PTS, while a positive association was found between exercise and some secondary endpoints.

Although most studies included exclusively active or former DVT patients, one of the studies included 50% of patients with causes of CVI other than a previous DVT.[27] This must be taken into account when analysing and comparing their results. Apart from the studies by Shrier et al., all studies were performed in <100 patients which is low when considering the high prevalence of DVT. The studies by Shrier et al. were performed in > 300 patients, although these were cohort studies and so did not randomize patients to intervention and control groups. The authors only recorded the levels of habitual activity. In the cohort study of Shrier just 71% of the patients reached the end of the 2-year follow up.[24] Strict in- and exclusion criteria (for example: exclusion of older patients, inclusion of only veterans or a fairly good tolerance to exercise) could also have influenced the outcomes, since this is not a representation of the average patient suffering from PTS. Moreover, of the included children in the pilot RCT 83% was overweight, which might have introduced significant bias in a study on physical activity. Lastly, exercise exposure among the trials was often not verified accurately.

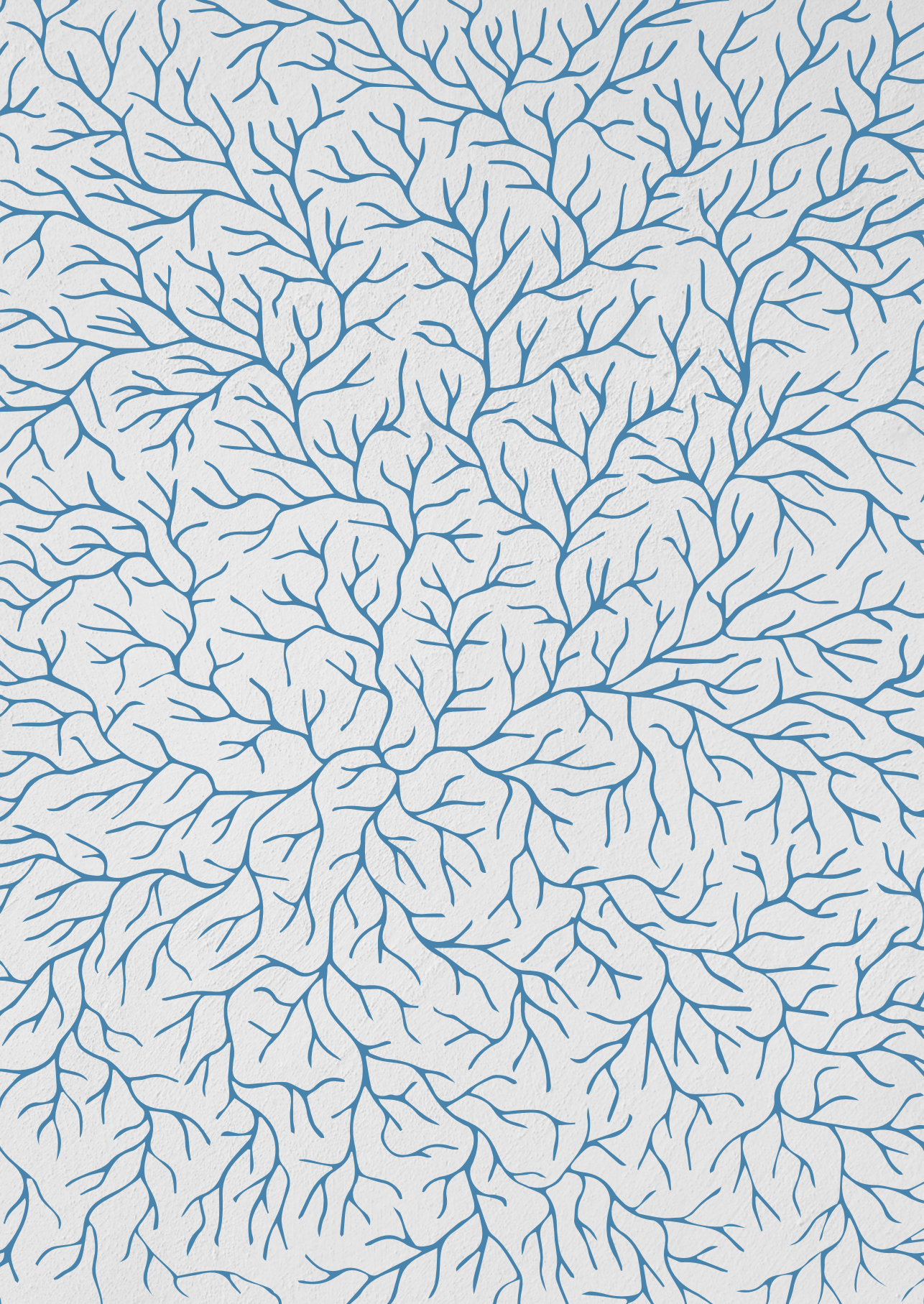
Conclusion

The relatively 'simple' intervention of exercise has positive effects in the acute and chronic phase after DVT, on both short and long term outcomes. A positive recommendation for treating PTS with a supervised exercise program, has been incorporated in the American Heart Association document on the prevention, diagnosis and treatment of PTS.[2] In analogy to peripheral arterial disease, physical exercise therapy could be a good supplementary therapy for DVT patients. Because patients may have an anxiety towards physical activity, especially when this temporarily increases pain or leg swelling, physicians should explicitly tell their patients exercise is not harmful. Further research is needed, focussing on the effects of different supervised exercise programs as part of the treatment for acute DVT as well as for patients suffering from PTS. With the upcoming popularity of activity tracking devices and the availability of apps, motivating patients to exercise and track lifestyle interventions may become much more easily accessible as well as more playful and fun.

REFERENCES

1. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost*. 2009 May;7(5):879-83.
2. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, Gupta DK, Prandoni P, Vedantham S, Walsh ME, Weitz JI; American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014 Oct 28;130(18):1636-61.
3. Kahn SR. The post-thrombotic syndrome. *Hematology Am Soc Hematol Educ Program.* 2016. 2;2016(1):413-418.
4. Lubberts B, Paulino Pereira NR, Kabrhel C, Kuter DJ, DiGiovanni CW. What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis. *Thromb Haemost.* 2016;116(3):417-31.
5. Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. *Phlebology*. 2018;33(3):163-184.
6. Caggiati A, De Maeseneer M, Cavezzi A, Mosti G, Morrison N.Rehabilitation of patients with venous diseases of the lower limbs: State of the art. *Phlebology*. 2018;33(10):663-671.
7. Williams KJ, Ayekoloye O, Moore HM, Davies AH. The calf muscle pump revisited. *J Vasc Surg Venous Lymphat Disord*. 2014 Jul;2(3):329-34
8. Trujillo-Santos J, Perea-Milla E, Jiménez-Puente A, Sánchez-Cantalejo E, del Toro J, Grau E, et al. Bed rest or ambulation in the initial treatment of patients with acute deep vein thrombosis or pulmonary embolism: findings from the RIETE registry. *Chest*. 2005 May;127(5):1631-6.
9. Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: a systematic review. *Thromb Res* 2008;122(6):763-773.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
11. Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. *Haemostasis*. 1994;24:158a
12. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000;31:1307-12
13. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg.* 2003;37:410–419.
14. McHorney CA, Ware JJE, Raczec AE. The MOS 36-item short form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and health constructs. *Med Care.* 1993 Mar;31(3):247-63.
15. Smith JJ, Garratt AM, Guest M, Greenhalgh RM, Davies AH. Evaluating and improving health-related quality of life in patients with varicose veins. *J Vasc Surg.* 1999 Oct;30(4):710-9.
16. Launois R. Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Quality Life Res* 1996;5:539-54

17. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci.* 1985;10:141–146
18. Yang AW, Li CG, Da Costa C, Allan G, Reece J, Xue CC. Assessing quality of case series studies: development and validation of an instrument by herbal medicine CAM researchers. J *Altern Complement Med 2009* May;15(5):513-522.
19. Jünger M, Diehm C, Störiko H, Hach-Wunderle V, Heidrich H, Karasch T, et al. Mobilization versus immobilization in the treatment of acute proximal deep venous thrombosis: a prospective, randomized, open, multicentre trial. *Curr Med Res Opin.* 2006 Mar;22(3):593-602
20. Blättler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. *Int Angiol.* 2003;22(4):393-400.
21. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. *Int Angiol* 2004;23(3):206-212.
22. Kahn SR, Azoulay L, Hirsch A, Haber M, Strulovitch C, Shrier I. Acute effects of exercise in patients with previous deep venous thrombosis: impact of the postthrombotic syndrome. *Chest* 2003;123(2):399-405.
23. Shrier I, Kahn SR. Effect of physical activity after recent deep venous thrombosis: a cohort study. *Med Sci Sports Exerc.* 2005 Apr;37(4):630-4.
24. Shrier I, Kahn SR, Steele RJ. Effect of early physical activity on long-term outcome after venous thrombosis. *Clin J Sport Med* 2009;19(6):487-49
25. Isma N, Johanssson E, Björk A, Björgell O, Robertson F, Mattiasson I, et al. Does supervised exercise after deep venous thrombosis improve recanalization of occluded vein segments? A randomized study. *J Thromb Thrombolysis* 2007;23(1):25-30
26. Kahn SR, Shrier I, Shapiro S, Houweling AH, Hirsch AM, Reid RD, et al. Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial. *CMAJ* 2011;183(1):37-44.
27. Padberg FT Jr, Johnston MV, Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. *J Vasc Surg.* 2004;39(1):79-87.
28. Hasan R, Hanna M, Zhang S, Malone K, Tong E, Salas N, et al. Physical activity in children at risk of postthrombotic sequelae: a pilot randomized controlled trial. *Blood Adv.* 2020 Aug 11;4(15): 3767-3775.
29. Roaldsen KS, Elfving B, Stanghelle JK, Talme T, Mattsson E. Fear-avoidance beliefs and pain as predictors for low physical activity in patients with leg ulcer. *Physiother Res Int.* 2009;14(3):167-180.
30. Kachroo S, Boyd D, Bookhart BK, LaMori J, Schein JR, Rosenberg DJ. Quality of life and economic costs associated with postthrombotic syndrome. *Am J Health Syst Pharm*. 2012 Apr 1;69(7):567-72.



Chapter 7

Feasibility of a treadmill test in patients with venous claudication in the work-up of endovenous stenting

Bram Rook
Elke M.G.J. de Jong
Ilse E.B.M. Kroft
Marie Josee E. van Rijn

A version of this chapter is submitted.

ABSTRACT

Background: Venous claudication (VC) remains an under-recognised condition, while the prevalence may be high.

Objectives: This case series aimed to evaluate the practicality of using a clinical treadmill test for patients with VC and to evaluate functional impairment of VC. We investigated whether VC could be provoked and recorded, and we assessed the utility of the parameters time and distance while performing a standardized treadmill test protocol before and after stenting.

Methods: A case series study was performed in patients with VC who were accepted for endovenous stent placement. Before and after stenting, the VEINES-QOL/Sym questionnaire and the Villalta score were conducted, the circumference of the affected leg was measured and a 20-minute treadmill test was performed. Primary outcomes were the time and distance of occurrence of symptoms and the absolute time and distance when symptoms prevented patients from continuing, and to compare these parameters before and after stenting.

Results: In all five patients, symptoms were successfully elicited during the treadmill test. During the first study visit, four out of five patients were unable to complete the test. By the second study visit, following stenting, improvements were observed across all treadmill test parameters. These changes were accompanied by a reduction in symptom severity and enhancements in quality of life. Leg circumference increased during the treadmill test before and after stenting.

Conclusion: This case series study showed that it is feasible to use a treadmill test as an instrument in patients suffering from VC, to assess functional impairment as well as the effect of venous stenting on functional impairment. A follow-up study is necessary to further investigate how accurate outcomes are in larger study populations with VC, what cut-of values could be used, and how a treadmill test may be applied as a screening instrument in patients with VC.

INTRODUCTION

Venous claudication (VC) is the feeling of tightness of the thigh or leg caused by an obstruction in the venous system. It is a symptom of post-thrombotic syndrome (PTS) resulting from long-term sequalae after deep venous thrombosis (DVT) of the lower extremities.[1,2] VC is believed to be more common after iliofemoral venous obstruction.[2,3] Its prevalence is unknown. One study found that the prevalence 4 years after the index DVT was 10.6% in a study among 85 patients with iliofemoral thrombosis.[4] Previous studies showed that increased outflow resistance, especially during exercise, increased venous pressure and volume in the lower leg.[2,5-7] As a consequence patients can experience tightness in the leg and thigh and even pain. Symptoms typically subside within 20 minutes in a period of rest or after elevation of the leg. For many patients severe VC is a major disability causing a significant decrease in quality of life (QOL).[2,4]

VC remains an understudied condition, and many healthcare providers treating patients with venous disease lack familiarity with this condition[3]. PTS is diagnosed with various scoring systems, such as the Villalta score, Venous Clinical Severity Score (VCSS) or CEAP classification.[8-10] VC is however not an item in any of these assessment tools.[11] While objective instruments like duplex ultrasonography can identify obstruction and reflux in veins[12], there is hardly any literature on methods to objectively and standardized diagnose and grade VC rather than patients' statements of tightness, soreness, paraesthesia and pain during exercise.[2,5,13] In patients eligible for venous stenting, the degree of PTS and the presence, type, location and degree of venous obstruction are taken into account, but seldomly the actual functional impairment.[13-15] Often, success of this procedure is assessed by patency of the stents, less frequent by improvement of QOL and almost never by improvement of walking distance.[14,15] However, up to 83% of patients report an improvement of VC after stenting when patients are interviewed.[16] This improvement has however not yet been adequately quantified.

In contrast, extensive data is available on treadmill testing for the assessment of arterial claudication.[16,17] This standardized treadmill test serves as a reliable tool for both diagnosing arterial claudication and evaluating the effectiveness of treatments. Parameters that are frequently used are the initial and absolute claudication time (ICT/ACT) and the initial and absolute claudication distance (ICD/ACD) during a standardized treadmill protocol.[17,18] For assessing VC this test is not used in current practice and only a few studies evaluated the prevalence of PTS and VC using a treadmill test.[2,4] Only one study assessed whether stenting of post-

thrombotic iliofemoral obstruction reduced venous hypertension while using a treadmill protocol together with invasive pressure measurements.[6]

The aim of this study was to determine whether VC could be provoked during a treadmill test, to evaluate the duration of the test (assessing its feasibility as a diagnostic tool in the outpatient clinic) and to examine the impact of stenting, specifically its potential to improve functional impairment.

METHODS

Study design

A pilot case series study was performed in a university medical centre. The medical ethical review board officially approved the study (METC ID: NL84143.078.23). All patients were informed by the recruiting physician and provided with an information letter. Written informed consent was obtained from all participants.

Participants

Patients ≥ 18 years of age with VC, who were scheduled for endovenous stenting, were evaluated for eligibility. Patients were only asked for participation after the decision for stenting was made. All patients had at least iliac, iliofemoral or caval obstruction and had to be able to perform a treadmill test. Patients with any other morbidity that mimicked similar symptoms, most of all arterial claudication, were not included. Moreover, prior vascular interventions for acute DVT, such as clot removal or stenting, were exclusion criteria. Due to the feasibility research design, we aimed to include five patients to assess the feasibility of incorporating a treadmill test into the work-up and follow-up of this patient group.

Primary and secondary objectives

The primary objective of this study was to assess the feasibility of a treadmill test in the work-up of VC patients. Specifically, we aimed to determine whether VC could be provoked and recorded, focusing on parameters such as the time and distance until the onset of symptoms, as well as the total time and distance covered. Secondary objectives included evaluating changes in VC following stenting by comparing and quantifying venous symptoms observed before and after the procedure. This assessment was conducted alongside other established venous parameters, such as QOL, leg circumference, and Villalta scores. Additionally, all patients were asked to rate their pain using a 0-10 numeric rating scale (NRS).

Study protocol

Patients were invited for the first visit which was scheduled before the stent procedure on a convenient moment for the patient. The second visit was scheduled approximately three months after stenting. During the first visit all baseline characteristics were collected. All patients completed the validated Dutch version of the VEINES-QOL/Sym questionnaire before the treadmill test and the Villalta score was recorded.[19] Before and after the treadmill test, the circumference of the affected leg was measured using a measuring tape. The circumference immediately just above the lateral malleoli at the ankle and mid-thigh were measured by the same physician. A measuring tape was used to determine the midthigh and the locations were marked. Patients were asked whether they recognised the symptoms during the treadmill test as their daily complaints.

The VEINES-QOL/Sym questionnaire

The VEINES-QOL/Sym is a tool to measure QOL in patients with venous disease of different origins.[20,21] The questionnaire consists of 26 items, including limitations in daily activities and psychological impact due to venous disease. The questionnaire gives two outcomes, one indicating QOL and one indicating symptom severity. If a patients scores a high result, this indicates a better and positive outcome.

Treadmill test protocol

The treadmill test (Treadmill custo er2100) was standardized and set at a continuous speed (3.2km/h) and inclination of 0% at the beginning according to the protocol based on the study of Kurstjens et al.[6] Each two minutes, the inclination was increased by 2% with a maximum of 10%. The patients were supervised during the test, without any stimulating encouragements. Participants were asked to walk until they experienced symptoms the recognised in their affected leg such as tightness, pain, fatigue, heaviness, cramps or stiffness. This was defined as the initial claudication distance (ICD) and initial claudication time (ICT). Patients were asked to continue the treadmill test until they were forced to stop due to the severity of symptoms or when they reached a maximum of 20 minutes. On this moment the absolute claudication distance (ACD) and the absolute claudication time (ACT) were noted. The distance was measured in meters and time in minutes and seconds. In addition, we asked patients if they could rate their pain on a 0–10 NRS to assess symptom severity during the test.

Analysis

All data were analysed using IBM SPSS Statistics Premium 'V 22. Nominal and continuous variables are represented as a number and frequency and mean ±

standard deviation, respectively. Both the total scores measured before and after stenting and the difference of the two study visits are presented in tables. Due to the small sample size we did not perform statistical analysis.

RESULTS

From September 2023 until December 2024, a total of seven patients participated in the study as shown in the flowchart in figure 1. There was a dropout of two patients due to comorbidity not related to the study (figure 1). Therefore, two other patients were enrolled in order to obtain pre- and post-stent outcomes for the anticipated number of five patients. There was missing data in one patient regarding the initial claudication time and distance. Baseline characteristics are shown in table 1.

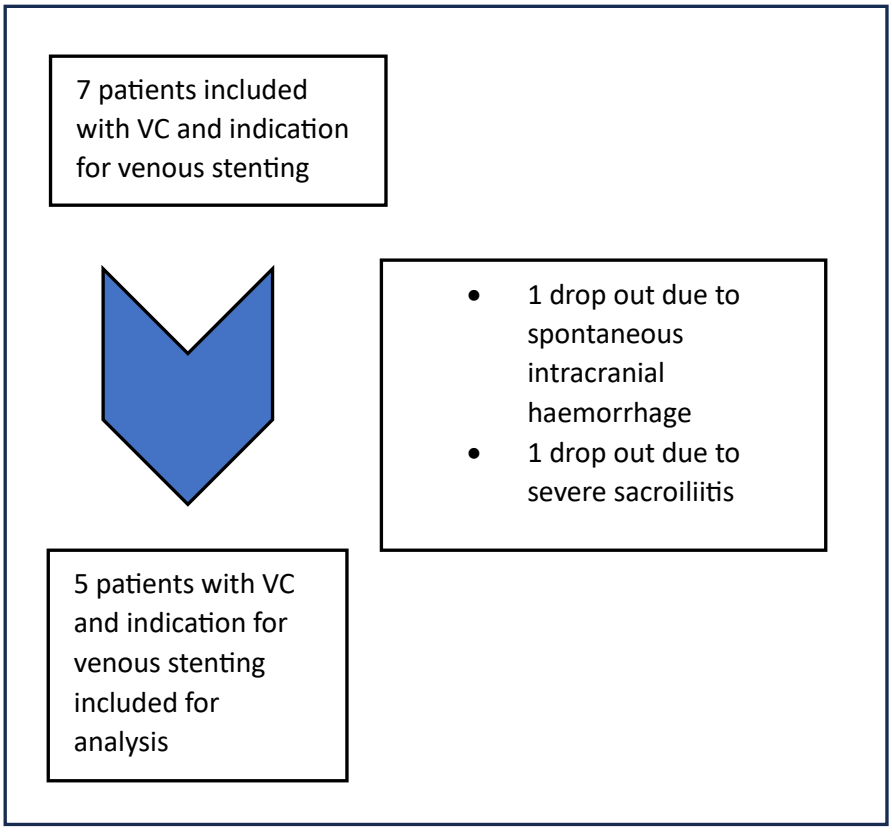


Figure 1: Flowchart of patient selection

Table 1: Baseline characteristics

Variables	n
Female, n (%)	4 (80)
Mean age, years	51.4
Mean BMI, kg/m^2	30.8
Mean time after DVT at 1st visit, months	40.3
Left-side obstruction, n (%)	3 (60)
Anticoagulation use, n (%)	5 (100)
Use of compression therapy, n (%)	4 (80)

BMI: body mass index; DVT: deep vein thrombosis.

Primary outcomes

The primary outcome measures of 1) the distance in meters, and the time in minutes and seconds, from the start of the investigation until the occurrence of symptoms and 2) the distance and time that compelled them to continue walking, are shown in table 2. Mean ICT improved from 01:35 minutes pre stent to 07:41 minutes post stent (+06:09), and mean ACT improved from 14:55 minutes pre stent to 17:17 minutes after stenting (+02:22). One patient indicated knee problems during the second study visit, affecting the treadmill test. Because this affected the test results, table 2 shows the results both including and excluding this patient. Four out of five patients did not finish the first treadmill test and had to terminate the test at a mean of 768 meters. At the second treadmill test, only one patient was not able to complete the test. The mean ACD was increased with 130 meters to 898 meters compared to the first test.

Secondary outcomes

All patients went down one Villalta category on the second visit compared to the first, with one patient scoring as no PTS and none scored as having severe PTS (table 3). The scores on both the VEINES-QOL and the VEINES-SYM questionnaires increased, indicating an improved QOL and decreased symptom severity, respectively. Four out of five (80%) patients recognised the complaints that were provoked during the treadmill test as their daily symptoms. On follow-up visits all patients had a 100% stent patency.

We compared leg circumference difference of the ankle and mid-thigh during treadmill test to investigate if we could demonstrate any difference in leg volume increase during walking, and if there was a difference after stenting. In all scenarios there was an increase in leg circumference of the affected leg after finishing the treadmill test. This slightly decreased after stenting (table 4).

Table 2: Claudication time and distance before and after stenting during treadmill test

Treadmill parameters	All patients (n = 5)			Exclusion of 1 patient (n = 4)		
	Before stent	After stent	Difference	Before stent	After stent	Difference
Mean initial claudication time, min:sec (SD)	01:35 (00:54)	07:41 (04:36)	06:09	01:16 (00:48)	09:03 (04:00)	07:47
Mean initial claudication distance, m (SD)	134 (91)	395 (240)	261	135 (105)	465 (211)	330
Mean absolute claudication time, min:sec (SD)	14:55 (03:23)	17:17 (06:07)	02:22	15:30 (03:53)	20:02 (00:02)	04:32
Mean absolute claudication distance, m (SD)	768 (182)	898 (320)	130	796 (213)	1042 (2.6)	246

SD: standard deviation

Table 3: Secondary outcome measures

		Before stent	After stent	Difference
Mean Villalta category	No PTS		1	n/a
	Mild PTS	1	3	n/a
	Moderate PTS	3	1	n/a
	Severe PTS	1		n/a
VEINES-QOL, mean (SD)		58 (10.9)	77.4 (15.6)	19.4
VEINES-SYM, mean (SD)		21.6 (4.7)	36 (9.9)	14.4

SD: standard deviation, n/a: not applicable

Table 4: Leg circumference affected leg

	Before treadmill (cm)	After treadmill (cm)	Increase during treadmill test
Mean size ankle pre stent (SD)	24.1 (1.6)	24.5 (1.2)	+0.4
Mean size ankle post stent (SD)	24.3 (1.6)	24.5 (2.2)	+0.2
Mean size mid-thigh pre stent (SD)	59.1 (5.7)	62.6 (7.2)	+3.5
Mean size mid-thigh post stent (SD)	59.3 (5.3)	62.6 (7.7)	+3.3

SD: standard deviation

DISCUSSION

This study demonstrated that a treadmill test assessing functional impairment of VC and effectivity of venous stenting is feasible. In all patients symptoms could be elicited consistent with VC. While 80% had to stop before the end of the first test, after stent placement 80% could complete the treadmill test. Time until symptoms increased after stenting, as did the absolute claudication time and distance.

The ICD before stent placement in our study population (134 m) was similar to results of the study from Delis et al. which was 130 m.[2] In that study, 17 out of 39 patients with previous iliofemoral thrombosis indicated VC with a median VCSS of six. In our study 80% of the patients were forced to terminate early before stenting (after 768m), whereas in the abovementioned study 15.4% had to discontinue the test (after 241m). However, the treadmill protocol used in the study of Delis et al was more intensive with a speed of 3.5km/h and a continuous 10% inclination in a maximum of 10 minutes. A protocol more similar to ours was used in the study of Kurstjens et al.[6] The mean pain free walking distance in that study, comparable to the ICD, was longer than in our study (289 m vs 134 m), whereas the mean walking distance, comparable to the ACD, (805 m vs 768 m) was similar.

There are different treadmill test protocols among studies investigating VC.[2,4,6] One study investigating PTS in 85 patients with a previous iliofemoral DVT used a standardized treadmill ergometry protocol to assess symptom-free walking distance. Patients had to continue the test only for 250 meters, but with a starting inclination of 10% and a speed of 3.2km/h.[4] This study found a prevalence of 10.6% of VC in their study population, but did not assess any other treadmill parameters. The study of Delis et al. used an inclination of 10% from the start as well.[2] The duration, speed and inclination of the treadmill test will impact the outcomes. Determining the appropriate protocol should be the subject of future studies. Furthermore it is important to establish the best mode of exercise provocation. One patient in our study indicated that he experienced more symptoms while walking on stairs then during the treadmill test. The first study that mentioned VC in 1967 used a 'stepping' test to elicit symptoms that imitated climbing stairs.[22] However, we could not find any literature where other devices then treadmills were used to study VC after DVT.

We asked patients to rate their pain on a 0-10 NRS scale to indicate symptom severity. However, all patients found it too difficult to define their symptoms precisely and rate the pain during walking. This shows the difficulty to formulate strict criteria for VC; the symptoms are diverse and differ between individuals or within the same patients on different times. In literature and guidelines there are no strict criteria on defining VC.[11,23] Other parameters such as the ICD and ACD could therefore be useful variables.[18] Other studies investigating VC using a treadmill test had similar ways of assessing symptoms.[2,6] Delis et al defined VC as 'persistent and uncomfortable tightness, ache, or pain in the thigh or calf which presented during the treadmill challenge, and worsened with exercise time'.[2] Since most patients recognised the symptoms during the test this could mean that a treadmill test could be used to measure functional impairment.[22]

The patients in our study were already accepted for endovascular stenting, indicating they had severe symptoms and were therefore expected to have limited distance and time on the treadmill device. However, the Villalta score of only one patient was quantified as severe, due to an active venous leg ulcer and three as moderate. The fifth patient with mild PTS would not have had an indication for endovenous stenting if it was not for the severe VC symptoms. In the study of Kurstjens et al., the mean numeric Villalta score was 2.0 ± 1.8 among 22 patients with VC.[6] These are relatively low Villalta scores and it shows the significance to screen for VC. The treadmill test may help identify affected patients and may support patient selection for endovenous stenting or monitor the effect of these costly interventions. The primary aim of the study of Kurstjens et al. was to investigate

haemodynamic effects of post-thrombotic obstructions after stenting with invasive pressure measurements during a treadmill test.[6] This method is essential to assess hemodynamics, but is not ideal for screening patient in an outpatient clinic setting. Our study therefore focussed on the parameters of the treadmill test itself. The length of the test might be a limitation for broader implementation. Especially for patients without, or with minor symptoms of VC, the test is probably not efficient. An option might be to use different protocols that are harder for patients but elicit symptoms earlier or use other devices such as a stair climber. Moreover, since endovascular stenting has more indications than VC, the test could be used only in patients with a low Villalta score, in that sense not eligible for stent placement, but who might benefit if diagnosed with VC. Another limitation of the current study design is the number of patients that were included, which limits generalizability. However, the results of this study can be useful for future research.

Clinical PTS scoring systems currently used measuring disease specific QOL or symptom severity include functional impairment.[9,24] Therefore, one can question the additional value of a treadmill test. However, when it comes to VC, none of these tools measure specifically the maximum pain free walking distance and thus the real functional impairment.[11] Although other studies showed that endovascular stenting has a positive effect on the QOL or VC[25,26], our study showed that a treadmill test can measure and quantify the effect of venous stenting on functional impairments of VC. Furthermore, if physicians only consider using the Villalta score or VCSS, the most common clinical scores used, patients with severe impairing VC might be missed.[9,11]

As anticipated, all parameters evaluated during the treadmill test on the second visit showed improvement, alongside enhancements in symptom severity, QOL, and Villalta score. These positive changes can be attributed to the beneficial impact of stent placement. All patient had a 100% patency at time of the second treadmill test and it is known that most patients report an improvement of VC after stenting.[15,27] In a time where evidenced based medicine and patient-oriented outcomes are increasingly important, the outcome of this test can be valuable for measuring the effect of stenting on functional outcomes rather than only stent patency.

One limiting factor in the use of a treadmill test is the presence of comorbidities. Various medical conditions can impact overall health, restrict musculoskeletal function, or produce symptoms that resemble VC. In our study, one patient experienced significant knee pain during the second visit, which may have led to an underestimation of the benefits of stenting. After evaluation, the symptoms

were deemed unrelated to the stent and attributed to a recent worsening of osteoarthritis. While comorbidities are common in the general population, they can introduce challenges in accurately diagnosing or assessing the severity of VC when using a treadmill test as a screening method. Comorbidity was also the reason that the total time of the study was longer than the six months that we anticipated. In addition to the two patients who dropped out of the study due to intracranial haemorrhage and sacroiliitis, there were additional patients not suitable for inclusion due to comorbidities affecting walking exercise, such as lumbago or neurological diseases.

In patients with arterial claudication exercise therapy significantly increases symptom free and total walking distance.[17,28] Individualized training programs also have a positive effect in patients with PTS.[29,30] For patients with VC this can be an alternative therapy to invasive stent treatment by improving exercise tolerance. Further investigation should evaluate if a treadmill test might be an instrument to guide and monitor this therapy. Meanwhile, research should also focus on developing PTS targeted supervised exercise programs. Further optimising this kind of exercise therapy might include treadmill testing combined with (non-) invasive venous pressure measurements[6,31] to evaluate hemodynamic effects of different training protocols.[32]

Conclusion

This first pilot case series research study demonstrated the feasibility of using a treadmill test as a tool for evaluating functional impairment in patients with VC and quantifying the impact of endovenous stenting. A follow-up study should focus on defining the most feasible treadmill protocol, determining cut-of values for diagnosing VC and which patients could be selected for stenting, before this test may be advised to be used in all patients with venous diseases. In addition, future research is needed to analyse how treadmill tests could monitor and/or improve exercise therapy in patients with VC.

Acknowledgements

The authors would like to thank Jennifer Heerings - 't Hart and Miranda van Zwieten (vascular diagnostics technicians at Erasmus Medical Centre) for their assistance in performing the treadmill tests.

REFERENCES

1. Kahn SR, Ginsberg JS. The post-thrombotic syndrome: Current knowledge, controversies, and directions for future research. *Blood Rev.* 2002 Sep;16(3):155-65.
2. Delis KT, Bountouroglou D, Mansfield AO. Venous Claudication in Iliofemoral Thrombosis: Long-term Effects on Venous Hemodynamics, Clinical Status, and Quality of Life. *Ann Surg.* 2004;239(1).
3. Tsouknidas I, Charisis N, Eklof B, Labropoulos N. Venous Claudication: a Scoping Review of the Pathophysiology and Clinical Importance. *Eur J Vasc Endovasc Surg*. 2022 Nov;64(5):535-543.
4. Nawasrah J, Zydek B, Lucks J, Renczes J, Haberichter B, Balaban Ü, et al. Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis - Results of the Iliaca-PTS - Registry. *Vasa*. 2021 Jan;50(1):30-37.
5. Tripolitis AJ, Milligan EB, Bodily KC, Strandness DE Jr. The physiology of venous claudication. *Am J Surg.* 1980 Mar;139(3):447-8.
6. Kurstjens RL, de Wolf MA, Konijn HW, Toonder IM, Nelemans PJ, de Graaf R, et al. Intravenous pressure changes in patients with postthrombotic deep venous obstruction: results using a treadmill stress test. *J Thromb Haemost.* 2016 Jun;14(6):1163-70.
7. Rosfors S, Blomgren L. Venous occlusion plethysmography in patients with post-thrombotic venous claudication. *J Vasc Surg.* 2013;58(3).
8. Vasquez MA, Munschauer CE. Venous clinical severity score and quality-of-life assessment tools: Application to vein practice. *Phlebology*. 2008;23(6):259-75.
9. Wik HS, Ghanima W, Sandset PM, et al. Scoring Systems for Postthrombotic Syndrome. Scoring Systems for Postthrombotic Syndrome. *Semin Thromb Hemost.* 2017;43(5).
10. Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. *Haemostasis*. 1994;24:158a
11. De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg.* 2022 Feb;63(2):184-267.
12. Raju S, Knepper J, May C, Knight A, Pace N, Jayaraj A. Ambulatory venous pressure, air plethysmography, and the role of calf venous pump in chronic venous disease. *J Vasc Surg Venous Lymphat Disord.* 2019;7(3).
13. Raju S, Fredericks R. Venous obstruction: An analysis of one hundred thirty-seven cases with hemodynamic, venographic, and clinical correlations. *J Vasc Surg.* 1991 Sep;14(3):305-13.
14. van Vuuren TMAJ, de Wolf MAF, Arnoldussen CWKP, Kurstjens RLM, van Laanen JHH, Jalaie H, et al. Editor's Choice – Reconstruction of the femoro-ilio-caval outflow by percutaneous and hybrid interventions in symptomatic deep venous obstruction. *Eur J Vasc Endovasc Surg.* 2017 Oct;54(4):495-503.
15. Morris RI, Pouncey AL, Quintana B, Khan T, Smith A, Saha P, et al. Quality of life outcomes for patients undergoing venous stenting for chronic deep venous disease. *J Vasc Surg Venous Lymphat Disord.* 2021 Sep;9(5):1185-1192.e2.
16. Majeed GM, Lodhia K, Carter J, Kingdon J, Morris RI, Gwozdz A, et al. A Systematic Review and Meta-Analysis of 12-Month Patency After Intervention for Iliofemoral Obstruction Using Dedicated or Non-Dedicated Venous Stents. *J Endovasc Ther.* 2022 Jun;29(3):478-492.

17. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: Walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis*. 2011 Sep;218(1):1-12.

18. van den Houten MM, Gommans LN, van der Wees PJ, Teijink JA. Minimally Important Difference of the Absolute and Functional Claudication Distance in Patients with Intermittent Claudication. *Eur J Vasc Endovasc Surg.* 2016 Mar;51(3):404-9.

19. van der Velden SK, Biemans AA, Nijsten T, Sommer A. Translation and validation of the Dutch VEINES-QOL/Sym in varicose vein patients. *Phlebology*. 2014 May;29(4):227-35.

20. Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. *J Clin Epidemiol.* 2006 Oct;59(10):1049-56.

21. Bland JM, Dumville JC, Ashby RL, Gabe R, Stubbs N, Adderley U, et al. Validation of the VEINES-QOL quality of life instrument in venous leg ulcers: Repeatability and validity study embedded in a randomised clinical trial. *BMC Cardiovasc Disord.* 2015 Aug 11;15:85.

22. Cockett FB, Thomas ML, Negus D. Iliac Vein Compression.—Its Relation to Iliofemoral Thrombosis and the Post-thrombotic Syndrome. *BMJ*. 1967;2(5543).

23. Perrin M, Eklof B, Van Rij A, Labropoulos N, Vasquez M, Nicolaides A, et al. Venous symptoms: The SYM Vein Consensus statement developed under the auspices of the European Venous Forum. *Int Angiol.* 2016 Aug;35(4):374-98.

24. Cleman J, Xia K, Haider M, Nikooie R, Scierka L, Romain G, et al. A state-of-the-art review of quality-of-life assessment in venous disease. *J Vasc Surg Venous Lymphat Disord.* 2024 Jul;12(4):101725.

25. Delis KT, Bjarnason H, Wennberg PW, Rooke TW, Gloviczki P. Successful iliac vein and inferior vena cava stenting ameliorates venous claudication and improves venous outflow, calf muscle pump function, and clinical status in post-thrombotic syndrome. *Ann Surg.* 2007 Jan;245(1):130-9.

26. Shekarchian S, Van Laanen J, Esmaeil Barbati M, Vleugels MJ, Nelemans P, Razavi MK, et al. Editor's Choice – Quality of Life after Stenting for Iliofemoral Venous Obstruction: A Randomised Controlled Trial with One Year Follow Up. *Eur J Vasc Endovasc Surg*. 2023 Nov;66(5):678-685.

27. de Wolf MA, de Graaf R, Kurstjens RL, Penninx S, Jalaie H, Wittens CH, et al. Short-Term Clinical Experience with a Dedicated Venous Nitinol Stent: Initial Results with the Sinus-Venous Stent. *Eur J Vasc Endovasc Surg.* 2015 Oct;50(4):518-26.

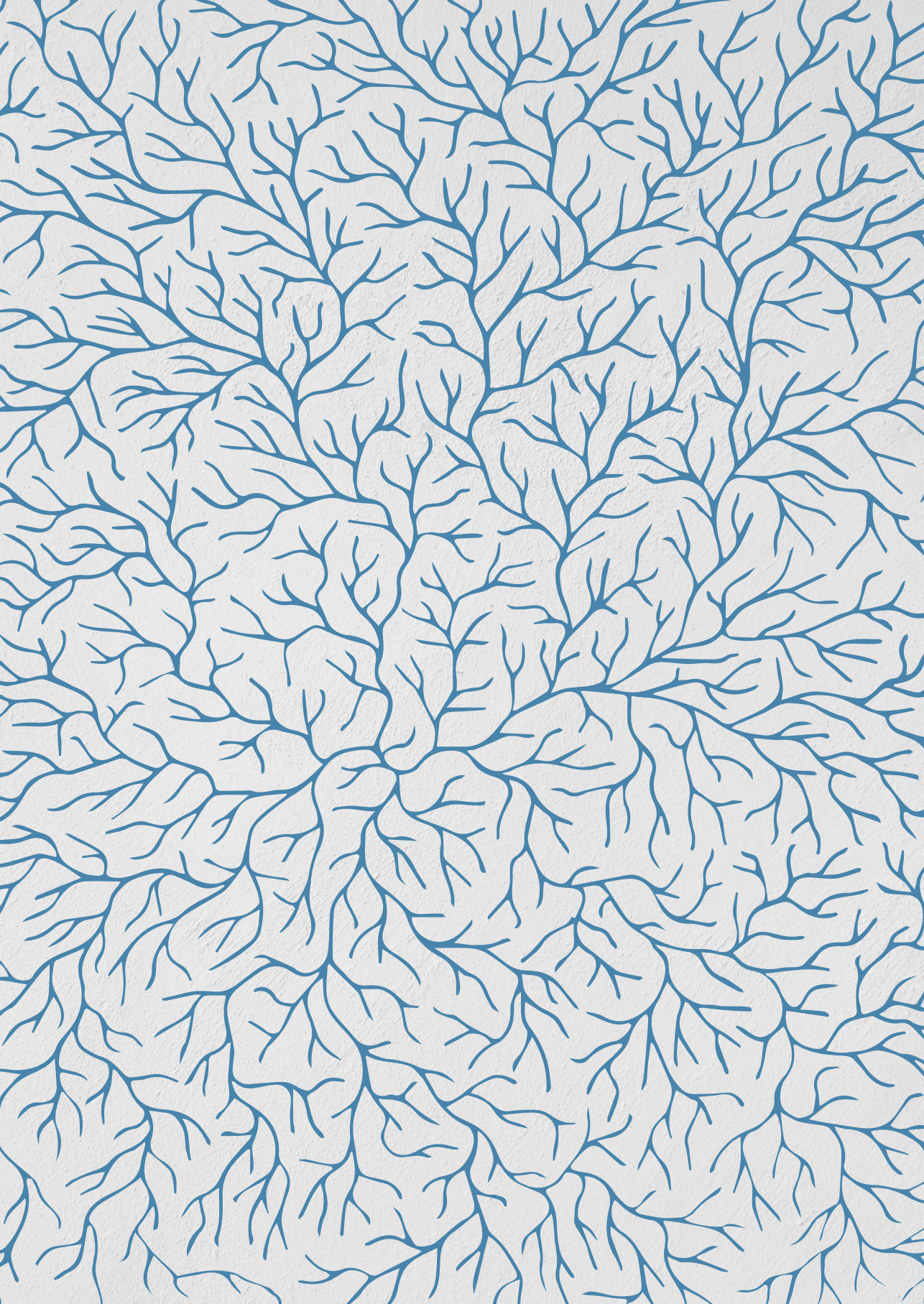
28. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on fitness and performance-based tests of function in intermittent claudication: A systematic review. *Sports Med.* 2013 Jun; 43(6):513-24.

29. Rook B, van Rijn MJE, Jansma EP, van Montfrans C. Effect of exercise after a deep venous thrombosis: A systematic review. *J Eur Acad Dermatol Venereol*. 2024 Feb;38(2):289-301.

30. Jasionowska S, Turner BRH, Machin M, Onida S, Gwozdz AM, Shalhoub J, et al. Systematic review of exercise therapy in the management of post-thrombotic syndrome. *Phlebology*. 2022 Dec;37(10):695-700.

31. Maleti O, Nicolaides A, Guerzoni S, Bergamo G, Lugli M. Residual volume fraction during walking using wireless air plethysmography in patients with chronic deep venous disease. *J Vasc Surg Venous Lymphat Disord.* 2022 Mar;10(2):423-429.e2.

32. Araujo DN, Ribeiro CT, Maciel AC, Bruno SS, Fregonezi GA, Dias FA. Physical exercise for the treatment of non-ulcerated chronic venous insufficiency. *Cochrane Database Syst Rev.* 2016 Dec 3;12(12):CD010637.



Chapter 8

General discussion

This thesis aimed to further strengthen the diagnostic process, prevention and treatment of the most serious presentations in chronic venous disease (CVD) care, namely venous leg ulcers (VLUs) in general and the post-thrombotic syndrome (PTS) after a previous deep venous thrombosis (DVT). Due to the wide variability in clinical characteristics and different etiologies underlying pathophysiology of the disease, there can be a diagnostic delay.[1] However, preventive measures, early recognition and treatment can alleviate symptoms and, most importantly, prevent the progression of the disease. The burden of CVD is high for society and for individual patients. Given the expected increase in incidence, this underlines the need to optimize CVD care. The challenge of improving both traditional outcomes, such as wound healing time, and patient-centred outcomes, such as quality of life (QOL), inspired this thesis. It focuses on enhancing the healthcare system and implementing preventive and treatment measures. This aim led to two main research questions, which will be discussed here:

- Does an efficient, evidence-based healthcare system result in improved patient-centred outcomes for venous leg ulcer care?
- Does optimizing the diagnostic process and conservative treatment options enhance the effectiveness of PTS care?

Part I
Does an efficient, evidence-based healthcare system result in improved patient-centred outcomes for venous leg ulcer care?

In the Netherlands, there is extensive experience with an efficient and effective primary care system involving general practitioners (GPs) and homecare organisations. In leg ulcer care, this system plays a crucial role in screening and treating leg ulcers. When wound healing is delayed or a specific treatable underlying cause is suspected, a referral to secondary care providers, such as a dermatologist or vascular surgeon, should be considered.[2,3] However, contrary to these current guidelines patients with leg ulcers can be referred late due to delays in follow-up, leading to disease progression, or due to misdiagnosing of an underlying cause.[1,4] Additionally, qualitative evidence-based protocols were sometimes outdated, and different organisations involved in ulcer care used varying guidelines.[5,6] It has previously been demonstrated that adequate knowledge, awareness, and use of evidence-based medicine protocols and guidelines, along with early recognition and diagnosis of underlying diseases and appropriate treatment measures, can improve outcomes.[7-10] At the turn of the century, community nursing clinics or specialized wound clinics were designed and introduced internationally to improve healing outcomes and continuity of care for all types of wounds.[11,12] In the Dutch

primary care system, and with the continuing trend for elderly patients to receive care at home as much as possible, such clinics were not introduced initially. Furthermore, adequate comparison of existing homecare organisations was not possible due to the lack of common guidelines. Subsequent studies on different care delivery systems demonstrated that the organisation of care is more significant than the exact location of care delivery, emphasising the importance of evidence-based medicine protocols.[12,13] In a joint directive of different Dutch healthcare associations, it was already recommended to implement multidisciplinary and specialized wound care systems, especially for more complicated wound care.[3] However, organisation of wound care remained fragmented throughout the country. This led to the creation of a new concept of ulcer care within the existing Dutch system, using evidence-based practices. This concept involved a one-stop clinic at the Dermatology Department in the ZGT Hospital, where a diagnosis was made and treatment plan was initiated at the first visit to the hospital after referral. Furthermore, nurses from two community care organisations were trained to visit patients at home to provide follow-up by up-to-date guidelines. The primary goal of this method was to create a clear and similar work-up for leg ulcer patients in the whole region of the study hospital that could lead to a decrease of time to wound closure. The complete concept and results of this new system are reported in Chapter 2. It describes the differences in outcomes of the periods before and after the introduction of this new method in a retrospective study. In line with previous studies, the rate of ulcer healing was improved through the introduction of the one-stop clinic, but time to wound closure was not statistically different between patients treated by specialized nurses compared to hospital care when adjusted for the effects of the one-stop clinic.[12,14] These positive effects are likely to occur due to the introduction of a evidenced based protocol and continuity of quality care out of hospital settings[15], although there seems no superior strategy for effective implementation of such protocols and guidelines.[16] The study was conducted retrospectively and patients that were included presented in different phases of the care management setup, including transitional phase from the old setting to the new setting. Although we did show positive results, these limitations confine the accuracy and generalizability of the results. Besides our initiatives, there are also other setups introduced, such as the Primary Care Plus (PC+) model (anderhalvelijnszorg/Stadspoli's). This system involves close cooperation between medical specialists and GPs. Patients visit medical specialists in healthcare facilities outside the hospital. The medical specialists provide treatment recommendations while the GP remains in charge of the management. However, a Dutch study on cost utility showed that this system was associated with an increase in the use of low-complex specialized care, instead of substitute expensive specialized care.[17]

Despite the need for new care models, home care will be even more important in the near future. There are more elderly people live at their own home (community dwelling elderly) and more of those people consist of frail elderly patients. These patients may have different treatment goals and a wound care model that takes into account appropriate care at home may be efficient. Our study showed similar wound closure time between home care and hospital care, which was in line with previous studies. This shows that follow-up VLU care is possible at homes of patients even in more complex situations after optimal treatment at the hospital.[12,14] However, optimal interdisciplinary cooperation between all parties involved is vital to succeed this.

To assess how our new healthcare concept could be further optimized, an evaluation of patient experience with the new one-stop clinic was performed in Chapter 3. A mixed qualitative and quantitative trial assessed symptoms, experiences, and preferences of a selected number of patients regarding the newly implemented method. Overall, patients appreciated the cooperation between GPs, homecare organisations, and the hospital. Some patients cited their preference for hospital care over home care, as they believed in the authority and superior knowledge of the hospital. In addition, patients chose specialized home care nurses over regular home care nurses. According to the theoretical domains framework from Weller used in this study, the patients' beliefs are covered by the 'knowledge' domain and 'beliefs about the consequences', emphasising the importance of patients' understanding of the treatment plan and the rationale behind it.[18] So, informing patients by trained healthcare workers might lead to increased adherence. The insights of this study highlight the need for evidence-based guidelines, quality training and cooperation with patients to increase their trust in the entire care system and thus improve compliance with treatment recommendations. Digital innovations assist in patient engagement by using applications that assist patients with education that can improve compliance. The use of digital innovation may further allow homecare professionals to contact experts easy when facing complex wounds which may increase effectiveness of these professionals.[19] Several telemedicine systems are already available in wound management such as teledermatology where patients can have their wounds assessed via a photo or via video consultations with healthcare professionals.[20,21]

Another topic that patients in the trial identified as important to address, besides wound healing, was pain management. Pain was the most impairing symptom and was indicated as the symptom that most interfered with daily life, so impairing QOL. This is in line with prior research focusing on different domains of life which

showed that VLUs were also associated with restricting social functioning, work capacity and psychologic well-being.[22-24] Assessing QOL as part of guideline-based treatment plans could assist healthcare workers to optimize therapy and the health status of patients by considering patients psychological, physical and social needs in a care plan which could increase cost-effectiveness.[25] Various patient reported outcome measures (PROMs) and health-related quality of life (HRQOL) instruments have been developed and used for CVD, although mainly for generic QOL and fewer for disease specific QOL, especially for VLUs. This makes it more difficult to compare research results regarding QOL.[26-28] Another difficulty in monitoring QOL in CVD is that clinical manifestations may differ considerably over time. The disease can therefore have varying impact on functional, aesthetic and social domains. This can be addressed by monitoring QOL with applications on patients' smartphones on a regular basis, additionally providing healthcare workers with up to date information. However, not all available questionnaires are validated for different population and languages. Optimal questionnaires provide valid data for a specific population, such as having only VLUs or only diabetic foot ulcers, and can be used over time.[29,30] Currently, there is no (inter)national consensus on which questionnaire should be used, and healthcare workers and researchers should consider their goals and specific patient groups when choosing a specific questionnaire. Recently, a short questionnaire, the Wound-QOL, has been validated in the Dutch population and can be used as a brief instrument for clinical use during the treatment of ulcers of mixed etiology.[31] Such usage of a standardized scoring system may improve inter-rater reliability among healthcare workers.

One of the secondary aims of the introduction of the one-stop clinic was cost reduction. In general, CVD has a large economic burden on healthcare system and recent studies estimate the annual costs may be as high as $3 billion per year in the United States alone.[32-34] This includes direct costs and indirect costs such as absenteeism. Due to differences of definitions and inability to identify indirect costs, the exact economic costs of CVD is difficult to investigate accurately. Others have analysed the economic burden of VLUs separately.[34-36] Published data varies widely from country to country, although there is a pattern of very expensive care. Identifying specific items for cost saving interventions remains a challenge as the care system is extensive, but previous research already showed that the implementation of a standardized leg ulcer pathway could help reduce costs.[33,37] In Chapter 4 the costs of the one-stop clinic implementation were evaluated. The costs were compared to the standard of care in other Dutch hospital. Because we hypothesized that implementing this new method would lead to fewer visits, the cost analysis focused on personnel costs and overhead costs. The results were in

line with other studies, showing the new method resulted in less costs which was attributed to fewer visits[36], although in our study, the mean days of treatment was remarkably higher in the research group. Personnel costs contributed significantly to the total amount VLU treatment, and thus fewer visit resulted in lower costs per person. However, the study had some important limitations in terms of methodology and generalizability. Although no patients in our trial were admitted, inpatient admission has been known to increase VLU costs significantly.[33] Hospital admission is often needed for treatment of infected VLU.[36] Both in hospital, ulcer clinics and in the home settings, infected VLUs are associated with far more use of resources. Healing rates and time to wound healing are increased in VLUs that are infected.[33,35,36,38] This emphasises the importance of accurate and early initial diagnosis, close monitoring of the healing process by skilled healthcare professionals who adapt treatment when appropriate, and identification and aggressive treatment of any infection to prevent hospital admissions and increased costs. Innovation and improvement in medical and surgical interventions entail economic costs but can further contribute to the cost-effective treatment.[39,40] As an example, early interventions as laser ablation of patients with VLUs showed faster VLU healing and lower VLU recurrence rates compared to deferred interventions, while also leading to more cost-effective care.[41,42] Digital innovation also creates new opportunities. Virtual visits have already been shown to be feasible for treating patients with varicose veins, with results comparable to traditional clinical visits.[43] Some studies demonstrate that specific digital interventions lead to positive cost utility and cost reduction, but further research is needed to corroborate these findings.[44]

Part II
Does optimizing the diagnostic process and conservative treatment options enhance the effectiveness of post-thrombotic syndrome care?

PTS can develop in up to half of all patients after a previous DVT and typically occurs within the first years.[45] In the last century, patients were prescribed strict bedrest after an acute DVT. Later, patients were treated with a continuous intravenous infusion of heparin and bedrest. In Europe, both types of treatment were complemented with leg compression, especially for symptom relieve. Compression therapy is thought to overcome venous hypertension and edema in the acute phase of PTS and reduce valvular reflux by improving the venous pump function of the calf.[46] Compression therapy is also associated with a reduction of PTS severity and venous ulcer recurrence.[47-50] Nowadays, the cornerstone of both DVT treatment and PTS prevention is early anticoagulation.[51] Known risk factors for developing PTS are residual thrombosis and recurrent DVT. Anticoagulation reduces these risk factors.

However, even with optimal anticoagulation, PTS cannot be prevented in all cases. Research has led to new treatment options such as early clot removal and stent placement in selected cases[52,53], but it has also been investigated whether existing therapies, such as compression therapy, could be optimized or more tailored to the individual patient.[54] Compression therapy has side effects including itching, skin irritation, and an unpleasant warm and moist feeling, while patients also have cosmetic objections. These factors contribute to poor adherence rates.[55] Adequate and efficient use largely depends on properly donning and doffing of stockings. Still, there is discussion on the duration of compression therapy to efficiently treat symptoms of an acute DVT and lower PTS incidence and severity. Furthermore, it is not clear if the routine use of compression therapy to prevent PTS in every patient is required. In a narrative review presented in Chapter 5 we described the clinical considerations in treating patients after DVT with compression therapy. We advocated that individualized therapy should only be applied by experienced healthcare workers who take physical signs and symptoms into account during follow-up. In this way, physicians can safely shorten the duration of compression therapy when no symptoms of PTS occur preventing overtreatment and discomfort, effectuating cost-reduction.[56]

Exercise therapy is a considered as treatment option for patients with CVD, especially in patients with a previous DVT, thus PTS, since this group had a clear moment of onset of the disease leading to CVD. The physiology of the venous function and the factors that contribute to it are becoming increasingly well understood, such as an optimal ankle function that stimulates venous return in the lower legs.[57] This understanding forms the basis of walking therapy, which could improve ankle function and increases calve muscle pump function. In the past, as previously discussed, patients with acute DVT were prescribed bedrest for fear of pulmonary embolism, but this concern later turned out to be unfounded.[58] Back in 2014, the American Heart association already recommended supervised exercise training program for patients with PTS[59-61], based on positive outcomes of a randomized controlled trial of Kahn[60] and the review of Kahn in 2008.[61] To evaluate the direct and long-term effects of physical activity in patients with an acute or previous DVT we conducted a systematic review of studies performed after Kahn's review.[62] The review presented in Chapter 6. In total 10 studies were included that were divided in three types of physical activity based on timing and duration; (1) early mobilization in the acute phase of the DVT; (2) short duration exercise one year after DVT and (3) prolonged exercise during follow-up after a previous DVT. Early mobilization after an acute DVT resulted to improvement of QOL and in pain reduction. After two years early mobilization resulted in a significant reduction

of PTS severity. Supervised exercise programs resulted in improvement of QOL as well. Furthermore, such programs showed reduction of symptoms of venous insufficiency. Physical activity after DVT is safe. Physicians should consider to instruct their patients that exercise is not harmful and may be beneficial. Nowadays it is also recommended to consider exercise in all patients with symptomatic CVD.[59] The role and optimal type of physical activity have not yet been established. Further research is warranted, with an emphasis on the optimization and efficacy of individual supervised exercise programs for patients with PTS and all patients with CVD. Activity tracking devices and availability of apps are emerging and accessible for all people. This can motivate patients to exercise and monitor and guide specific lifestyle interventions.

It remains a challenge to offer patients with advanced PTS effective treatment. Patients with critical symptoms such as recurrent VLUs or severe venous claudication (VC) may benefit from endovenous stenting when there is a significant obstruction.[63-65] VC is a common symptom of PTS reported by patients, presenting as discomfort or pain when walking or climbing stairs. If patients that indicate VC are diagnosed with significant venous stenosis they should be considered for venous stenting.[52,66] However, there is still a lack of knowledge and data how to classify symptoms correctly and how indicated symptoms of VC are correlated with the degree of physical activity, such as distance and time of walking. Furthermore, it is unknown what the exact effect is on these parameters after treatment with endovascular stenting. The pilot case series described in Chapter 7 aimed to observe and quantify clinical symptoms during a treadmill test before and after venous stenting for VC. The study demonstrated that, even within the limits of a pilot study, using a treadmill test assessing functional impairment and effectivity of venous stenting can be feasible in individual patients. Though it is known that most patients report an improvement of VC after stenting, this study showed that outcomes as distance and time of a treadmill test objectively improved after stenting. For the entire group of patients with PTS it is not clear whether a treadmill test is useful and accurate, as there are many other factors that can influence the outcomes, such as comorbidity.[52,67,68] However, when it comes to VC, none of the existing scoring systems contain VC as an entity or measure specifically the maximum pain free walking distance and thus real functional impairment.[59] Moreover, only relying on the Villalta score or the venous clinical severity score (VCSS), the most common clinical scores used, patients with severe impairing VC might be missed.[59,69] Another study using treadmill diagnose VC found a mean numeric Villalta score of only 2.0 among 22 patients with VC.[70] These relatively low Villalta scores underscores the need of screening for VC, mainly by questioning patients. An exercise test can assist in identifying patients affected by VC. Further understanding

of the pathophysiology of VC is necessary to elucidate the mechanisms contributing to symptomatic VC and the impact of venous stenting. Future clinical trials should assess how accurate the outcomes are in a bigger study population of patients with VC, what cut-off values could be used, and how a treadmill test may be used as a screening instrument.

Future perspectives

The research presented in this thesis focused on optimizing diagnostics and treatment methods in CVD management, with a focus on individual patients and patient-oriented outcomes. In addition, it provides insight into various challenges that CVD patients and physicians face in the clinical course of the disease. The findings in this thesis contribute to overall CVD management. However, the high burden of CVD for individual patients and healthcare budgets and the expected increase in incidence underscore that further research is warranted. Digital and technical innovations are increasingly emerging and are changing the nature of research and can contribute to improve clinical management and cost reduction. Big data and artificial intelligence play a central role in this trend. Since electronic patients records (EPRs) are widely and increasingly used in healthcare we have the ability to collect vast amounts of valuable data. Machine learning programs and artificial intelligence can subsequently recognise complex patterns to enhance prediction, diagnosis and monitor treatment effects.[71] This may be especially useful in patients with CVD, as this is a heterogeneous group of signs and symptoms associated with the presence of chronic venous insufficiency (CVI). The first predictive models for PTS using machine learning are already developed.[72] Such models will gradually be integrated into EPRs, which will provide physicians with timely information so they can take early actions. This will not only benefit dermatological care, but healthcare in general.[20,73] Predictive risk models can help physicians to identify patients at risk of delayed treatment or of disease progress and furthermore increase the effectiveness of therapy, especially when it comes to lifestyle diseases with modifiable risk factors. Treating physicians should consider lifestyle interventions through lifestyle coaches or digital applications to help patients cope with these factors. Various factors that increase the risk of disease progression of CVD or delayed VLU healing can be addressed, such as immobility, smoking, obesity or diet. It can be challenging for patients to follow such lifestyle interventions, like following exercise programs of several months. The rising popularity of activity tracking devices, wearables and healthcare applications can help assist both patients to adhere to treatment recommendations and also physicians to motivate and guide these patients. Educating and coaching patients on lifestyle should be done as early as possible to maximize future effects.

In addition to lifestyle interventions, digital innovation creates an opportunity to enhance patient engagement and efficiency of treatment. As an example integrating PROMs as the Villalta score and QOL or symptom severity questionnaires into healthcare applications may optimize prognostication and patient selection for check-up visits. A workup in which DVT patients complete such PROMs annually combined with applications on patients smartphones that can recognise skin changes may for example automatically create clinical scores that assist physicians in monitoring their patients. With these scores we can effectively select those patients who are likely to develop PTS, investigate these patients early and treat them aggressively to prevent disease progression. A challenge to implementation is ensuring that patients maintain the motivation and priority to keep up with annual PROMs, especially if they are not experiencing symptoms

Increasing patient engagement can be achieved by providing a better interface between patients and healthcare workers and current digital information, for example using ChatGPT.[20,74-76] Such programs can provide relevant information to patients in a more understandable textual context. It is important that the conditions for digital care are used safely and properly. We must ensure that AI programs identify and use the most relevant and reliable sources and that ICT are safe and well-functioning and that integration of digital care into existing work processes is guaranteed.[74] This is already a challenge and will be even more challenging in an era of increasing use of digital systems.

Besides digital innovation, basic (patho)physiological studies will still be needed to further understand mechanisms responsible or contributing to symptomatic CVD or CVD progress.[77] Understanding such mechanisms could contribute to improve certain treatments. As an example, understanding the physiology of walking and the venous system might lead to more viable targets for treatment as exercise programs.[57,59] Furthermore, some techniques such as dedicated venous stents to treat stenotic and occluded veins are rather new and already have promising results.[52,63,68,78] Future clinical studies in these innovative techniques can help to develop even better stents or make the technique possible for more indications and patients. Besides stenting in PTS, acute DVTs are also a target for intervention. A recent conducted meta-analysis of four recent RCTs examining effectiveness of early thrombus removal compared to anticoagulation alone showed an overall positive effect on the risk of any PTS. Due to some limitations and heterogeneity in the selected studies including a significantly increased risk of major bleedings, it is not advisable to recommend the procedure in all cases. However, the findings resulted in a recommendation to consider this procedure in selected patients

presenting with an acute DVT.[53] This is significant because it highlights the direct need for comprehensive diagnostics to assess affected venous segments in all new DVT patients to consider their suitability for aggressive early thrombus removal interventions.[79]

People can develop venous pathology at any age, however, with the aging population it is expected to have an increase of elderly and thus more frail patients. Especially the older elderly are more at risk of cognitive impairment, polypharmacy, a limited life expectancy, immobility, a poor nutritional status and multimorbidity, which can all influence disease progression and affect care management. The group of vulnerable elderly patients are considered as frail. Trivial stressor events can result in disproportionate health changes in frail older patients and a considerable impact on QOL.[80] Tailoring therapy goals is important in this group to both contribute to maintaining QOL and sustainable healthcare costs. Different assessment and screening tools are available to identify frail older patients.[80] The use of these instruments in combination with PROMs and subsequent shared-decision making with patients, family and physicians like GPs, geriatric physicians, dermatologists and vascular surgeons, might lead to a limited but tailored management plan that avoids expensive hospital care. This approach of appropriate care (in Dutch: 'Passende Zorg') is stimulated by the Dutch government, although literature to guide treating physicians in specific diseases is limited.[81] Future research should determine the optimal care of CVD and feasibility within this patient group and whether it is beneficial by evaluating over- and undertreatment and healthcare costs. In addition to more frail older people, there is also a tendency of community dwelling in the Netherlands, i.e. older adults living within their own house that are less likely to move to healthcare facilities. The follow-up of patients with CVD and in particular VLUs in the home setting is often more challenging whereas patients in specific healthcare facilities are usually more easier to approach by institutional physicians and nurses. The described interdisciplinary collaboration of the new ulcer care method in Chapter 2 where educated and experienced nurses and GPs can easily discuss patients with medical specialists is a good example to enhance and strengthen homecare of frail elderly CVD patients in the near future. Another option that is interesting to improve the efficiency of CVD care is live consultation with dermatologists at healthcare institutions such as nursing homes.[82] There may be several benefits, such as vulnerable patients not having to visit the outpatient clinic and dermatologists being able to obtain more contextual information from patients and the healthcare institution to provide tailored treatment advice.

Because treatment of venous insufficiency has been shown to lead to faster wound healing and fewer recurrences, patients require early investigation to assess etiology and appropriate treatment options. A comprehensive guideline from 2018, supported by various involved healthcare associations, on the organisation of wound care in the Netherlands (Kwaliteitsstandaard Organisatie van wondzorg in Nederland), recommended referral of patients within a maximum of three weeks to an expert team if wound healing is delayed or deteriorated.[3] However, these recommendations are still not included in other guidelines such as the current guidelines on VLUs from 2010 of the Dutch GPs network. This guideline still recommends referral of only those patients with VLUs, among others indications, if there is no healing tendency after two months of treatment or if there is doubt about the venous origin.[6] Since CVD care requires a multidisciplinary approach, sharing updated guidelines is essential. Local initiatives such as the experience of the one-stop clinic contributes to earlier referral but ideally, such healthcare systems should be recommended in guidelines that are shared and supported by all stakeholders in CVD management. Further research may evaluate the preferred way to implement a multidisciplinary, standardized and futureproof healthcare system for CVD management nationwide. It may also identify any barriers that have hindered the implementation of such systems in the past or may hinder implementation the future.

REFERENCES

1. Probst S, Saini C, Gschwind G, Stefanelli A, Bobbink P, Pugliese MT, et al. Prevalence and incidence of venous leg ulcers-A systematic review and meta-analysis. *Int Wound J.* 2023 Nov;20(9):3906-3921.
2. Richtlijn Veneuze pathologie 2023 NVDV.
3. Kwaliteitsstandaard Organisatie van wondzorg in Nederland. 2018.
4. Zorginstituut Nederland. Evaluatie standpunt 2014 en afsprakendocument 2017 over invasieve behandeling van varices - 2021.
5. NHG-Standaard Varices (M30). 2009.
6. NHG-Standaard Ulcus cruris venosum (M16). 2010.
7. Atkin L, Schofield A, Kilroy-Findley A. Updated leg ulcer pathway: Improving healing times and reducing costs. *Br J Nurs.* 2019 Nov 14;28(20):S21-S26.
8. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, et al. Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT. *Health Technol Assess.* 2019 May;23(24):1-96.
9. Van Hecke A, Grypdonck M, Defloor T. A review of why patients with leg ulcers do not adhere to treatment. *J Clin Nurs.* 2009 Feb;18(3):337-49.
10. Weller CD, Richards C, Turnour L, Team V. Understanding factors influencing venous leg ulcer guideline implementation in Australian primary care. *Int Wound J.* 2020 Jun;17(3):804-818
11. Manu CA, Mustafa OG, Bates M, Vivian G, Mulholland N, Elias D. Transformation of the multidisciplinary diabetic foot clinic into a multidisciplinary diabetic foot day unit: Results from a service evaluation. *Int J Low Extrem Wounds.* 2014 Sep;13(3):173-9.
12. Harrison MB, VanDenKerkhof E, Hopman WM, Graham ID, Lorimer K, Carley M. Evidence-informed leg ulcer care: A cohort study comparing outcomes of individuals choosing nurse-led clinic or home care. *Ostomy Wound Manage.* 2011 Aug;57(8):38-45.
13. Harrison MB, Graham ID, Lorimer K, Vandenkerkhof E, Buchanan M, Wells PS, et al. Nurse clinic versus home delivery of evidence-based community leg ulcer care: A randomized health services trial. *BMC Health Serv Res.* 2008 Nov 26;8:243.
14. Harrison MB, Graham ID, Lorimer K, Friedberg E, Pierscianowski T, Brandys T. Leg-ulcer care in the community, before and after implementation of an evidence-based service. *CMAJ.* 2005 May 24;172(11):1447-52.
15. Sili A, Zaghini F, Monaco D, Dal Molin A, Mosca N, Piredda M, et al. Specialized Nurse-led Care of Chronic Wounds During Hospitalization and After Discharge: A Randomized Controlled Trial. *Adv Skin Wound Care.* 2023 Jan 1;36(1):24-29.
16. Kerr J, Devane D, Ivory J, Weller C, Gethin G. Effectiveness of implementation strategies for venous leg ulcer guidelines: A systematic review. *J Tissue Viability.* 2020 Aug;29(3):161-168.
17. van den Bogaart EHA, Spreeuwenberg MD, Kroese MEAL, Ruwaard D. Substitution or addition: An observational study of a new primary care initiative in the Netherlands. *J Health Serv Res Policy.* 2023 Jul;28(3):157-162.
18. Weller CD, Richards C, Turnour L, Patey AM, Russell G, Team V. Barriers and enablers to the use of venous leg ulcer clinical practice guidelines in Australian primary care: A qualitative study using the theoretical domains framework. *Int J Nurs Stud.* 2020 Mar;103:103503.

19. Sood A, Granick MS, Trial C, Lano J, Palmier S, Ribal E, et al. The role of telemedicine in wound care: A review and analysis of a database of 5,795 patients from a mobile wound-healing center in Languedoc-Roussillon, France. *Plast Reconstr Surg.* 2016 Sep;138(3 Suppl):248S-256S.
20. Jonnagaddala J, Godinho MA, Liaw ST. From telehealth to virtual primary care in Australia? A Rapid scoping review. *Int J Med Inform.* 2021 Jul;151:104470
21. Chen L, Cheng L, Gao W, Chen D, Wang C, Ran X. Telemedicine in chronic wound management: Systematic review and meta-analysis. *JMIR Mhealth Uhealth.* 2020 Jun 25;8(6):e15574.
22. Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes.* 2007 Jul 25;5:44.
23. Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: A systematic review. *J Wound Care.* 2014 Dec;23(12):601-12.
24. Phillips P, Lumley E, Duncan R, Aber A, Woods HB, Jones GL, et al. A systematic review of qualitative research into people's experiences of living with venous leg ulcers. *J Adv Nurs*. 2018 Mar;74(3):550-563.
25. Cheng Q, Gibb M, Graves N, Finlayson K, Pacella RE. Cost-effectiveness analysis of guideline-based optimal care for venous leg ulcers in Australia. *BMC Health Serv Res.* 2018 Jun 7;18(1):421.
26. Liu S, Team V, Qiu Y, Weller CD. Investigating quality of life instrument measurem ent properties for adults with active venous leg ulcers: A systematic review. *Wound Repair Regen.* 2022 Jul;30(4):468-486.
27. Lurie F, Passman M, Meisner M, Dalsing M, Masuda E, Welch H, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord.* 2020 May;8(3):342-352.
28. Venkatraman P, Anand S, Dean C, Nettleton R, Sawi A, Afify S. Pilot study investigating the feasibility of an ulcer-specific quality of life questionnaire. *Phlebology*. 2005;20:14-27
29. de Almeida ILGI, Figueiredo PHS, Silva WT, Mendonça VA, Lacerda ACR, Lima VP, et al. Reliability and validity of specific quality of life assessment questionnaires related to chronic venous insufficiency: a systematic review. *J Vasc Bras.* 2022 Oct 24;21:e20210229.
30. Cleman J, Xia K, Haider M, Nikooie R, Scierka L, Romain G, et al. A state-of-the-art review of quality-of-life assessment in venous disease. *J Vasc Surg Venous Lymphat Disord.* 2024 Jul;12(4):101725.
31. Amesz SF, Klein TM, Meulendijks AM, Nguyen TV, Blome C, Roodbol PF, et al. A translation and preliminary validation of the Dutch Wound-QOL questionnaire. *BMC Dermatol.* 2020 Aug 26;20(1):5.
32. Kim Y, Png CYM, Sumpio BJ, DeCarlo CS, Dua A. Defining the human and health care costs of chronic venous insufficiency. *Semin Vasc Surg.* 2021 Mar;34(1):59-64.
33. Phillips CJ, Humphreys I, Thayer D, Elmessary M, Collins H, Roberts C, et al. Cost of managing patients with venous leg ulcers. *Int Wound J.* 2020 Aug;17(4):1074-1082.
34. Kolluri R, Lugli M, Villalba L et al. An estimate of the economic burden of venous leg ulcers associated with deep venous disease. Vasc Med. 2022 Feb;27(1):63-72.
35. Kolluri R, Lugli M, Villalba L, Varcoe R, Maleti O, Gallardo F, et al. Health economic burden that different wound types impose on the UK's National Health Service. *Int Wound J.* 2017 Apr; 14(2):322-330.
36. Ma H, O'Donnell TF Jr, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. *J Vasc Surg Venous Lymphat Disord*. 2014 Oct;2(4):355-61.
37. Atkin L, Schofield A, Kilroy-Findley A. Updated leg ulcer pathway: Improving healing times and reducing costs. *Br J Nurs.* 2019 Nov 14;28(20):S21-S26.

38. National Institute for Health and Care Excellence (NICE). Varicose veins: diagnosis and management Clinical guideline [Internet]. 2013, reviewed in 2016. Available from: www.nice.org.uk/guidance/cg168 [accessed 18 December 2024]

39. Rognoni C, Lugli M, Maleti O, Tarricone R. Venous stenting for patients with outflow obstruction and leg ulcers: Cost-effectiveness and budget impact analyses. *J Comp Eff Res.* 2020 Jul;9(10): 705-720.

40. Epstein D, Bootun R, Diop M, Ortega-Ortega M, Lane TRA, Davies AH. Cost-effectiveness analysis of current varicose veins treatments. *J Vasc Surg Venous Lymphat Disord.* 2022 Mar;10(2): 504-513.e7.

41. Gohel MS, Mora MSc J, Szigeti M, Epstein DM, Heatley F, Bradbury A, et al. Long-term Clinical and Cost-effectiveness of Early Endovenous Ablation in Venous Ulceration: A Randomized Clinical Trial. *JAMA Surg*. 2020 Dec 1;155(12):1113-1121.

42. Epstein DM, Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, et al. Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. *Br J Surg.* 2019 Apr;106(5):555-562

43. Lin JC, Mclaughlin D, Zurawski D, Kennedy N, Kabbani L. Comparison of virtual visit versus traditional clinic for management of varicose veins. *J Telemed Telecare.* 2020 Jan-Feb;26(1-2):100-104.

44. de la Torre-Díez I, López-Coronado M, Vaca C, Aguado JS, de Castro C. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: A systematic review. *Telemed J E Health*. 2015 Feb;21(2):81-5

45. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The postthrombotic syndrome: Evidence-based prevention, diagnosis, and treatment strategies: A scientific statement from the American heart association. *Circulation*. 2014 Oct 28;130(18):1636-61.

46. Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. *Phlebology*. 2018 Apr;33(3):163-184.

47. Milic DJ, Zivic SS, Bogdanovic DC, Golubovic MD, Lazarevic MV, Lazarevic KK. A randomized trial of class 2 and class 3 elastic compression in the prevention of recurrence of venous ulceration. *J Vasc Surg Venous Lymphat Disord.* 2018 Nov;6(6):717-723.

48. Finlayson K, Edwards H, Courtney M. The impact of psychosocial factors on adherence to compression therapy to prevent recurrence of venous leg ulcers. *J Clin Nurs.* 2010 May; 19(9-10):1289-97.

49. Van Hecke A, Grypdonck M, Defloor T. Interventions to enhance patient compliance with leg ulcer treatment: A review of the literature. *J Clin Nurs.* 2008 Jan;17(1):29-39

50. Shi C, Dumville JC, Cullum N, Connaughton E, Norman G. Compression bandages or stockings versus no compression for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2021 Jul 26;7(7):CD013397.

51. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021 Dec;160(6):e545-e608

52. Shekarchian S, Van Laanen J, Esmaeil Barbati M, Vleugels MJ, Nelemans P, Razavi MK, et al. Editor's Choice – Quality of Life after Stenting for Iliofemoral Venous Obstruction: A Randomised Controlled Trial with One Year Follow Up. *Eur J Vasc Endovasc Surg.* 2023 Nov;66(5):678-685.

53. Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur J Vasc Endovasc Surg.* 2021 Jan;61(1):9-82.

54. Ten Cate-Hoek AJ, Bouman AC, Joore MA, Prins M, Ten Cate H; IDEAL DVT trial investigators. The IDEAL DVT study, individualised duration elastic compression therapy against long-term duration of therapy for the prevention of post-thrombotic syndrome: protocol of a randomised controlled trial. *BMJ Open.* 2014 Sep 4;4(9):e005265.
55. Bar L, Brandis S, Marks D. Improving Adherence to Wearing Compression Stockings for Chronic Venous Insufficiency and Venous Leg Ulcers: A Scoping Review. *Patient Prefer Adherence.* 2021 Sep 17;15:2085-2102.
56. Amin EE, Ten Cate-Hoek AJ, Bouman AC, Meijer K, Tick L, Middeldorp S, et al. Individually shortened duration versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome: a cost-effectiveness analysis. *Haematol*. 2018 Jan;5(1):e25-e33.
57. Caggiati A, De Maeseneer M, Cavezzi A, Mosti G, Morrison N. Rehabilitation of patients with venous diseases of the lower limbs: State of the art. *Phlebology*. 2018 Dec;33(10):663-671.
58. Trujillo-Santos J, Perea-Milla E, Jiménez-Puente A, Sánchez-Cantalejo E, del Toro J, Grau E, et al. Bed rest or ambulation in the initial treatment of patients with acute deep vein thrombosis or pulmonary embolism: Findings from the RIETE registry. *Chest*. 2005 May;127(5):1631-6.
59. De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg.* 2022 Feb;63(2):184-267.
60. Kahn SR, Shrier I, Shapiro S, Houweling AH, Hirsch AM, Reid RD, et al. Six-month exercise training program to treat post-thrombotic syndrome: A randomized controlled two-centre trial. *CMAJ*. 2011 Jan 11;183(1):37-44
61. Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: A systematic review. *Thromb Res.* 2008;122(6):763-73.
62. Rook B, van Rijn MJE, Jansma EP, van Montfrans C. Effect of exercise after a deep venous thrombosis: A systematic review. *J Eur Acad Dermatol Venereol.* 2024 Feb;38(2):289-301
63. Majeed GM, Lodhia K, Carter J, Kingdon J, Morris RI, Gwozdz A, et al. A Systematic Review and Meta-Analysis of 12-Month Patency After Intervention for Iliofemoral Obstruction Using Dedicated or Non-Dedicated Venous Stents. *J Endovasc Ther.* 2022 Jun;29(3):478-492.
64. Nawasrah J, Zydek B, Lucks J, Renczes J, Haberichter B, Balaban Ü, et al. Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis - Results of the Iliaca-PTS - Registry. *Vasa*. 2021 Jan;50(1):30-37.
65. Delis KT, Bountouroglou D, Mansfield AO. Venous Claudication in Iliofemoral Thrombosis: Long-term Effects on Venous Hemodynamics, Clinical Status, and Quality of Life. *Ann Surg.* 2004 Jan; 239(1):118-26.
66. Villalba LM, Bayat I, Dubenec S, Puckridge P, Thomas S, Varcoe R, et al. Review of the literature supporting international clinical practice guidelines on iliac venous stenting and their applicability to Australia and New Zealand practice. *J Vasc Surg Venous Lymphat Disord.* 2024 Sep;12(5):101843.
67. de Wolf MA, de Graaf R, Kurstjens RL, Penninx S, Jalaie H, Wittens CH, et al. Short-Term Clinical Experience with a Dedicated Venous Nitinol Stent: Initial Results with the Sinus-Venous Stent. *Eur J Vasc Endovasc Surg.* 2015 Oct;50(4):518-26.
68. Morris RI, Pouncey AL, Quintana B, Khan T, Smith A, Saha P, et al. Quality of life outcomes for patients undergoing venous stenting for chronic deep venous disease. J Vasc *Surg Venous Lymphat Disord.* 2021 Sep;9(5):1185-1192.e2.
69. Wik HS, Ghanima W, Sandset PM, Kahn SR. Scoring Systems for Postthrombotic Syndrome. *Semin Semin Thromb Hemost*. 2017 Jul;43(5):500-504.

70. Kurstjens RL, de Wolf MA, Konijn HW, Toonder IM, Nelemans PJ, de Graaf R, et al. Intravenous pressure changes in patients with postthrombotic deep venous obstruction: results using a treadmill stress test. *J Thromb Haemost.* 2016 Jun;14(6):1163-70.

71. Butova X, Shayakhmetov S, Fedin M, Zolotukhin I, Gianesini S. Artificial Intelligence Evidence-Based Current Status and Potential for Lower Limb Vascular Management. *J Pers Med.* 2021 Dec 2;11(12):1280.

72. Wu Z, Li Y, Lei J, Qiu P, Liu H, Yang X, et al. Developing and optimizing a machine learning predictive model for post-thrombotic syndrome in a longitudinal cohort of patients with proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2023 May;11(3):555-564.e5.

73. Willis VC, Thomas Craig KJ, Jabbarpour Y, Scheufele EL, Arriaga YE, Ajinkya M, et al. Digital Health Interventions to Enhance Prevention in Primary Care: Scoping Review. *JMIR Med Inform.* 2022 Jan 21;10(1):e33518.

74. Beheshti L, Kalankesh LR, Doshmangir L, Farahbakhsh M. Telehealth in Primary Health Care: A Scoping Review of the Literature. *Perspect Health Inf Manag*. 2022 Jan 1;19(1):1n. P

75. Athavale A, Baier J, Ross E, Fukaya E. The potential of chatbots in chronic venous disease patient management. *JVS Vasc Insights.* 2023;1:100019.

76. Kiernan A, Boland F, Moneley D, Doyle F, Harkin DW. Varicose Vein Education and Informed coNsent (VVEIN) study: a randomised controlled pilot feasibility study. *Ann Vasc Surg.* 2024 Sep; 106:142-151.

77. Nicolaides A, Kakkos SK, Estrada-Guerrero JG. Chronic venous disease: What if everything started with early care? A discussion with experts. *Phlebology*. 2024 Sep;39(8):509-511.

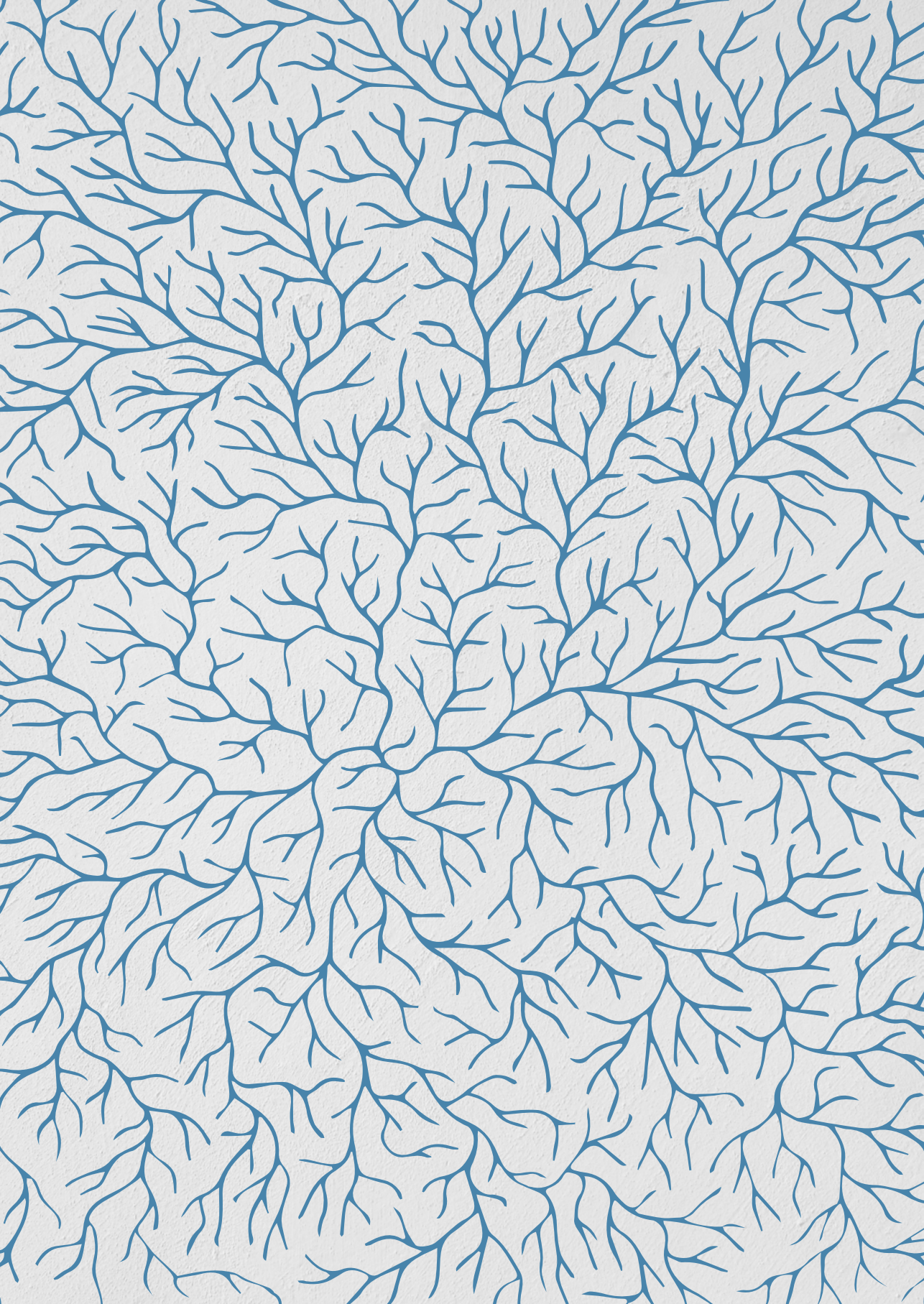
78. Williams ZF, Dillavou ED. A systematic review of venous stents for iliac and venacaval occlusive disease. *J Vasc Surg Venous Lymphat Disord.* 2020 Jan;8(1):145-153.

79. Meissner MH, Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, et al. Early thrombus removal strategies for acute deep venous thrombosis: Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2012 May;55(5):1449-62.

80. Lubeek SFK. Geriatric dermatology: optimising care in frail older adults. 2017. Dissertation.

81. Zorginstituut Nederland. Adviesrapport Samenwerken aan passende zorg de toekomst is nu – published 27-11-2020.

82. Lubeek SF, Van Der Geer ER, Van Gelder MM, Van De Kerkhof PC, Gerritsen MJ., et al. Dermatologic care of institutionalized elderly patients: A survey among dermatologists in the Netherlands. *Eur J Dermatol.* 2015 Nov-Dec;25(6):606-12.



APPENDIX

- Dutch summary (Nederlandse samenvatting)
- Research data management
- Abbreviations
- Supplementary tables
- Acknowledgements (Dankwoord)
- About the author (Curriculum Vitae)
- Portfolio

Nederlandse samenvatting

Chronisch veneuze ziekte (CVZ) bestaat uit verschillende soorten aandoeningen die als gemeenschappelijk kenmerk hebben dat het veneuze systeem van het lichaam is aangedaan, in de meeste gevallen zijn dit de benen. Een bekend voorbeeld zijn spataderen. Deze aandoening geeft allerlei verschillende klachten variërend van pijn, kramp, verkleuringen van de huid tot zelfs chronische wonden. Door deze klachten heeft de ziekte een grote impact op de patiënten, zowel functioneel als psychisch waardoor de kwaliteit van leven wordt aangetast. Daarnaast heeft CVZ een grote maatschappelijke impact en zorgt het voor hoge zorgkosten. CVZ is een van de meest voorkomende medische problemen in de wereld. Door de groeiende wereldwijde bevolking en ook een steeds ouder wordende bevolking is de verwachting dat nog veel meer mensen in de toekomst CVZ zullen krijgen.

Om de CVZ goed te onderzoeken is het nodig te begrijpen hoe een veneus bloedvat is opgebouwd. Veneuze bloedvaten zorgen er voor dat bloed terug stroomt naar het hart. Om te zorgen dat bloed terug kan stromen tegen de zwaartekracht in hebben deze bloedvaten kleppen die zorgen dat het bloed alleen maar één kant op kan stromen. Onder andere door te lopen en je kuitspier aan te spannen wordt het bloed als het ware weer terug gepompt naar het hart.

De bloedvaten kunnen op verschillende manieren en op verschillende plekken beschadigd raken. Zo kunnen er bij de geboorte al problemen zijn met de aanleg van bloedvaten of zorgt genetische aanleg voor het ontwikkelen van de ziekte gedurende het leven. In de meeste gevallen is het niet exact bekend wat de oorzaak van CVZ is. Er zijn echter een hoop risicofactoren bekend die de kans op het ontwikkelen van CVZ verhogen. Staande beroepen, veel zitten, vrouwelijk geslacht, ouderdom en obesitas zijn bekende risicofactoren die zijn geassocieerd met CVZ. De gedacht is dat door chronische ontstekingsprocessen er allerlei veranderingen optreden van de bloedvaten en de omliggende weefsels. Bloedvaten kunnen hierdoor slapper worden of kunnen kleppen kapot gaan. Een belangrijke andere oorzaak is het ontwikkelen van een bloedprop in het been, oftewel een trombosebeen. Hierdoor kunnen kleppen in de bloedvaten direct kapot gaan of kan schade door chronische ontsteking op langere termijn ontstaan. De schade op langere termijn wordt in dit geval van een trombosebeen het posttrombotisch syndroom genoemd. Al deze oorzaken zorgen uiteindelijk er voor dat bloed minder goed terug naar het hart stroomt, het bloed in de bloedvaten in de benen langer blijft staan en er daardoor een grote bloeddruk ontstaat in de bloedvaten. Dit wordt veneuze hypertensie, oftewel verhoogde veneuze bloeddruk, genoemd. Dit

zorgt voor verdere veranderingen in alle weefsels, waardoor er op langere termijn problemen spataderen ontstaan, vocht in de benen maar eventueel ook wonden van de huid.

Er bestaan verschillende behandelopties voor CVZ, welke afhankelijk zijn van de oorzaak. Zo dragen veel mensen steunkousen om tegendruk te geven, zodat door de verhoogde bloeddruk in de bloedvaten minder snel vocht door de wand van het bloedvat lekt en er verdere schade ontstaat. Spataderen kunnen zelf ook behandeld of zelfs verwijderd worden. Maar ook bij mensen met een trombosebeen direct het bloedpropje oplossen door invasieve ingrepen of het slikken van bloedverdunners zijn opties om verdere schade te voorkomen. Wat een groeiende focus heeft binnen wetenschappelijk onderzoek naar CVZ is levensstijl. Veel bekende risicofactoren ontstaan door toenemende welvaart, welke dus mogelijke doelen zijn van onderzoek en behandeling. Afvallen en bewegingstherapie zijn hier belangrijke onderdelen.

Ondanks groeiende inzichten en nieuwe behandelopties bestaan er nog verschillende uitdagingen in de zorg van CVZ. De klachten die patiënten aangeven staan soms niet in verhouding met de ernst van schade van de bloedvaten of hebben overlap met andere aandoeningen. Goed onderzoek naar de oorzaak en de ernst van de aandoening zodra patiënten zich melden is dus belangrijk om snel met de juiste therapie te starten, maar ook om te voorkomen dat de ziekte in de loop van de tijd verergert, zogenaamde preventieve zorg.

Het doel van dit proefschrift was om te onderzoeken of 1) een efficiënter en op wetenschappelijk bewijs gebaseerd zorgsysteem leidt tot betere patiëntgerichte uitkomsten in de zorg voor veneuze been ulcera/zweren (chronische wonden) en 2) of het optimaliseren van het diagnostische proces en conservatieve behandelingsopties leidt tot een verbetering van de effectiviteit van zorg voor mensen met het posttrombotisch syndroom.

In hoofdstuk 2 hebben wij een nieuwe opzet van patiënten met beenulcera zorg onderzocht. Het concept werd bedacht naar aanleiding van onderzoeken dat het gestructureerd organiseren zorg gebaseerd op wetenschappelijke onderzoeken zou zorgen voor betere uitkomsten. Hiervoor werd een systeem bedacht waar patiënten die naar de dermatoloog werden verwezen vanuit de eerste lijn, zoals huisartsen, tijdens het eerste bezoek in het ziekenhuis direct onderzoek kregen naar de oorzaak en er een behandelplan werd opgesteld. Als de behandeling thuis kon plaatsvinden werden speciaal opgeleide verpleegkundigen ingezet om samen

met de huisarts de behandeling over te nemen en de wonden te behandelen. Zij konden op ieder moment contact konden opnemen met de dermatoloog in het ziekenhuis voor extra advies.

De studie was opgezet om te onderzoeken of er een verschil was in tijd tot wondgenezing voor patiënten met veneus beenulcus die worden behandeld door gespecialiseerde verpleegkundigen in vergelijking met behandeling door verpleegkundigen in een ziekenhuisomgeving. Wij vonden echter dat de tijd tot wondgenezing niet verschillend tussen patiënten die werden behandeld door zulke gespecialiseerde verpleegkundigen in vergelijking met ziekenhuiszorg, wanneer gecorrigeerd voor de effecten van de het nieuwe systeem, ook wel de one-stop-kliniek genoemd. Wij vonden wel dat na introductie van de one-stop-kliniek de snelheid tot het genezen van de wond verbeterde en de kans op genezing van beenulcera dus werd vergroot. We verwachten dat de positieve effecten waarschijnlijk optraden door effectief georganiseerde zorg en het snel starten van een behandeling.

Om te onderzoeken wat de patiënten van de nieuwe opzet van zorg vonden, hebben we in hoofdstuk 3 patiënten geïnterviewd en gevraagd een vragenlijst in te vullen over hun idee van de nieuwe opzet. Zij gaven aan dat zij de samenwerking tussen alle verschillende hulpverleners waardeerden. Ook werd er aangegeven dat zij meer vertrouwen hadden in zorgverleners als zij meer specialistischere kennis hadden, zoals dermatologen of de gespecialiseerde verpleegkundigen. Uit dit onderzoek bleek ook dat pijn was het meest beperkende symptoom was en werd aangemerkt als het symptoom dat het meest van invloed was op het dagelijks leven.

Om te beoordelen om of deze studie ook kosteneffectief zou zijn, staat in hoofdstuk 4 het onderzoek waarin dit onderzocht is. We gingen ervan uit dat de implementatie van deze nieuwe methode zou leiden tot minder bezoeken aan hulpverleners, de kostenanalyse richtte zich dan ook op personeelskosten en overheadkosten. De resultaten waren in lijn met andere onderzoeken, wat aantoonde dat de nieuwe methode zou kunnen leiden tot lagere kosten, wat wij toeschrijven aan minder bezoeken aan het ziekenhuis Aangezien dit een kleine studie was gericht op specifieke kosten en CVD ook leidt tot veel andere, indirecte kosten zoals werkverzuim, kunnen deze resultaten niet gegeneraliseerd worden.

In hoofdstuk 5 hebben we ons gericht om te onderzoeken hoe lang compressie-therapie zoals steunkousen gebruikt moeten worden om effectief te zijn bij patiënten na een diep veneuze trombose (DVT). Geacht wordt dat deze therapie

symptomen kan verbeteren, maar ook het risico op het ontwikkelen van lange termijn klachten zoals het posttrombotisch syndroom kan verminderen. In het literatuuronderzoek zijn we dieper op onderzoeken van anderen ingegaan om dit te onderzoeken. We beschrijven in de studie de klinische overwegingen bij het behandelen van patiënten DVT met compressietherapie. We pleitten dat therapie alleen zou mogen worden geïndividualiseerd en dus eventueel verkort wanneer ervaren zorgverleners die tijdens de follow-up patiënten goed in de gaten houden dit bepalen. Op deze manier kunnen artsen de duur van compressietherapie veilig verkorten wanneer er geen symptomen van PTS zijn, waardoor overbehandeling en teveel ongemak worden vermeden. Een eerdere studie door andere onderzoekers vond dat op deze manier kosten bespaard worden.

In een ander literatuuronderzoek in hoofdstuk 6 hebben we onderzocht wat de directe en de lange termijn effecten zijn van lichaamsbeweging bij patiënten met een acuut DVT of een eerder doorgemaakt DVT. We onderzochten tien studies die wij opdeelden naar wanneer de lichaamsbeweging, meestal in de vorm van specifieke bewegingstherapieën werden uitgevoerd. We vonden dat patiënten na een acute DVT weer vroeg gingen mobiliseren dit resulteerde in verbetering van de levenskwaliteit en in pijnvermindering. Na twee jaar resulteerde zulke vroege mobilisatie in een belangrijke vermindering van de ernst van PTS. Langdurige oefenprogramma's onder begeleiding van instructeurs resulteerden ook in verbetering van de levenskwaliteit. We stellen dan ook dat lichamelijke oefening na een DVT is veilig is en artsen zouden moeten overwegen om hun patiënten met een acuut DVT te instrueren dat bewegen en sporten gunstig kan zijn voor hun prognose en niet gevaarlijk is.

Het blijft een uitdaging om patiënten met ernstigere vormen van PTS effectieve behandeling te bieden. Een onderdeel van de klachten na een trombose been is veneuze claudicatio (VC). Dit is een veelvoorkomend symptoom dat door patiënten wordt aangegeven als ongemak of pijn bij het lopen of traplopen. Er is echter nog steeds een gebrek aan kennis en gegevens over hoe symptomen correct moeten worden geclassificeerd en hoe symptomen van VC samenhangen met de mate van fysieke activiteit, zoals afstand en tijd van lopen. Bovendien is het onbekend wat het exacte effect is op afstand en duur van lopen na behandeling met endovasculaire stents. In hoofdstuk 7 hebben we onderzocht welke en na hoe lang en hoe ver lopen op een loopband de symptomen ontstaan. Dit onderzochten wij zowel voor als na het plaatsen van een veneuze stent. De studie toonde aan dat, zelfs binnen de grenzen van deze kleine studie, het gebruik van een loopbandtest om functionele beperkingen en effectiviteit van veneuze stents te beoordelen

haalbaar kan zijn bij individuele patiënten. Voor de hele groep patiënten met VC is het echter niet duidelijk of een loopbandtest nuttig en nauwkeurig is, aangezien er veel andere factoren zijn die de uitkomsten kunnen beïnvloeden, zoals andere ziekten of conditie. Verder onderzoek zal moeten uitwijzen of dit onderzoeksmiddel ook geschikt is om bij grote groepen patiënten en wat de consequenties zijn van de uitkomsten.

De onderzoeken die in dit proefschrift worden gepresenteerd richten zich op het identificeren van onderwerpen voor het optimaliseren van diagnostiek en behandelmethoden bij de behandeling van CVZ, waarbij aandacht werd besteed aan individuele patiënten en patiëntgerichte uitkomsten. We hebben laten zien dat een goed georganiseerde methode van zorg belangrijk is om wondgenezing te versnellen en waarschijnlijk ook zorg voor lagere kosten. Ook laten we zien dat het individualiseren van zorg een steeds belangrijke rol speelt binnen CVZ zorg. Hoewel compressietherapie nog steeds de hoeksteen van de behandeling van CVZ, zullen andere therapievormen, waaronder oefentherapie in combinatie met de opkomst van digitale innovaties, zorgen voor positieve impuls binnen CVZ zorg.

Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. All studies described in this thesis were conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). The studies in Chapter 2, 3 and 3 were not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) and were waived ethical approval due to the nature of the study by the committees for local feasibility of scientific research at the ZGT hospital and the Deventer hospital. The recognised Medical Ethics Review Committee 'METC Erasmus Medical Centre', Rotterdam, the Netherlands has reviewed and given approval to conduct the study described in Chapter 7. Furthermore, written informed consent was obtained from all participating patients included in Chapter 7. For the interviews in Chapter 3, respondents were informed that the results will be used for publication. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage, when applicable).

Data collection and storage

For Chapter 7 data were collected through electronic Case Report Forms (eCRF) using CASTOR EDC or with paper CRFs. From Castor EDC or from the paper CRFs data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA. For Chapter 2, 3 and 4 all anonymous data that was collected from electronic patient files was locally stored at the on the department server in the ZGT hospital and was password protected that was only accessible by project members working at the ZGT hospital. Paper (hardcopy) data are stored in cabinets on the science department of de ZGT Hospital (interviews) and the surgery department of the Erasmus medical centre according to data regulations. Written informed consents, paper CRFs, questionnaires and patient identification keys of the study described in Chapter 7 are stored at the surgery department within the hospital premises.

Availability of data

The studies are both published with open and without open access. The data will be archived for 15 years after termination of the study. Reusing the data for future research is only possible after a permission of the researches. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

Abbreviations

ABPI	Ankle-brachial pressure index
CEAP (classification)	Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification
CVD	Chronic venous diseases
CVI	Chronic venous insufficiency
DVT	Deep vein thrombosis
EMLA	Eutectic mixture of local anaesthetics
GP	General practitioner
HRQOL	Health-related quality of life
NSAID	Non-steroid anti-inflammatory drug
PTS	Post-thrombotic syndrome
PROMs	Patient reported outcome measures
TBI	Toe-brachial index
VAS	Visual analogue scale
VC	Venous claudication
VCSS	Venous clinical severity score
VEINES-QOL/Sym	Venous Insufficiency Epidemiological and Economic Study Quality of Life/symptoms
VTE	Venous thromboembolism
VLU	Venous leg ulcer
VV	Varicose vein
QOL	Quality of life

Supplementary tables

Supplementary Table I: Complete search strategy of Chapter 6 Effect of exercise after a deep venous thrombosis: a systematic review.

Update of search: article *Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: a systematic review. Thromb Res. 2008;122(6):763-73. doi: 10.1016/j.thromres.2007.10.011. Epub 2007 Dec 21. PMID: 18078981.*

Date of search:	:14-03-2022
Databases:	
PubMed	: 994
EMBASE.com	: 2160
Total	: 3154
After deduplication	: 2406

PubMed

#1 DVT

"Thromboembolism"[Mesh:NoExp] OR "Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh:NoExp] OR "Venous Insufficiency"[Mesh] OR Phlebothrombos*[tiab] OR Venous Thrombos*[tiab] OR Deep Vein Thrombos*[tiab] OR Deep-Venous Thrombos*[tiab] OR Deep-Vein Thrombos*[tiab] OR Postthrombotic syndrome[tiab] OR postthrombosis syndrome[tiab] OR post thrombosis syndrome[tiab] OR post thrombotic syndrome[tiab] OR postthrombophlebitic syndrome[tiab] OR "Venous Stasis Syndrome"[tiab] OR DVT[tiab] OR VTE[tiab] OR deep thrombophlebitis[tiab] OR "Venous Insufficien*"[tiab] OR "insufficient vein"[tiab] OR "vein insufficien*"[tiab] OR "venous incompetence"[tiab] OR "Pulmonary Embolism"[Mesh:NoExp] OR "Pulmonary Embolism*"[tiab] OR "Pulmonary Thromboembolism*"[tiab] OR "Postphlebitic Syndrome*"[tiab] OR "Postphlebitic Disease*"[tiab] OR "Postphlebitic Ulcer*"[tiab] OR "post-phlebitic syndrome*"[tiab]

#2 Physical activity

"Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Early Ambulation"[Mesh] OR Exercis*[tiab] OR "Physical Activ*"[tiab] OR physical fitness[tiab] OR "Walking"[Mesh] OR walk*[tiab] OR "Running"[Mesh] OR run[tiab] OR running[tiab] OR jog[tiab] OR jogging[tiab] OR ambulation[tiab]

#3 RCT

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controll*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])

Search	PubMed Query 14-03-2022	Results
#6	Search: **#3 AND #4** Filters: **from 2007/7/1 - 3000/12/12**	994
#5	Search: **#3 AND #4**	1,670
#4	Search: **(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controll*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])**	7,256,050
#3	Search: **#1 AND #2**	3,127
#2	Search: **"Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Early Ambulation"[Mesh] OR Exercis*[tiab] OR "Physical Activ*"[tiab] OR physical fitness[tiab] OR "Walking"[Mesh] OR walk*[tiab] OR "Running"[Mesh] OR run[tiab] OR running[tiab] OR jog[tiab] OR jogging[tiab] OR ambulation[tiab]**	764,950
#1	Search: **"Thromboembolism"[Mesh:NoExp] OR "Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh:NoExp] OR "Venous Insufficiency"[Mesh] OR Phlebothrombos*[tiab] OR Venous Thrombos*[tiab] OR Deep Vein Thrombos*[tiab] OR Deep-Venous Thrombos*[tiab] OR Deep-Vein Thrombos*[tiab] OR Postthrombotic syndrome[tiab] OR postthrombosis syndrome[tiab] OR post thrombosis syndrome[tiab] OR post thrombotic syndrome[tiab] OR postthrombophlebitic syndrome[tiab] OR "Venous Stasis Syndrome"[tiab] OR DVT[tiab] OR VTE[tiab] OR deep thrombophlebitis[tiab] OR "Venous Insufficien*"[tiab] OR "insufficient vein"[tiab] OR "vein insufficien*"[tiab] OR "venous incompetence"[tiab] OR "Pulmonary Embolism"[Mesh:NoExp] OR "Pulmonary Embolism*"[tiab] OR "Pulmonary Thromboembolism*"[tiab] OR "Postphlebitic Syndrome*"[tiab] OR "Postphlebitic Disease*"[tiab] OR "Postphlebitic Ulcer*"[tiab] OR "post-phlebitic syndrome*"[tiab]**	141,966

EMBASE.com

#1 DVT

'thromboembolism'/de OR 'venous thromboembolism'/de OR 'vein thrombosis'/de OR 'vein insufficiency'/exp OR Phlebothrombos*:ti,ab OR 'Venous Thrombos*':ti,ab OR 'Deep Vein Thrombos*':ti,ab OR 'Deep-Venous Thrombos*':ti,ab OR 'Deep-Vein Thrombos*':ti,ab OR 'Postthrombotic syndrome':ti,ab OR 'postthrombosis syndrome':ti,ab OR 'post thrombosis syndrome':ti,ab OR 'post thrombotic syndrome':ti,ab OR 'postthrombophlebitic syndrome':ti,ab OR 'Venous Stasis Syndrome':ti,ab OR DVT:ti,ab OR VTE:ti,ab OR 'deep thrombophlebitis':ti,ab OR 'Venous Insufficien*':ti,ab OR 'insufficient vein':ti,ab OR 'vein insufficien*':ti,ab OR 'venous incompetence':ti,ab OR 'Pulmonary Embolism*':ti,ab OR 'Pulmonary Thromboembolism*':ti,ab OR 'Postphlebitic Syndrome*':ti,ab OR 'Postphlebitic Disease*':ti,ab OR 'Postphlebitic Ulcer*':ti,ab OR 'post-phlebitic syndrome*':ti,ab

#2 Physical activity

'exercise'/exp OR 'kinesiotherapy'/exp OR 'mobilization'/exp OR Exercis*:ti,ab OR 'Physical Activ*':ti,ab OR 'physical fitness':ti,ab OR 'walking'/exp OR walk*:ti,ab OR 'running'/exp OR run:ti,ab OR running:ti,ab OR jog:ti,ab OR jogging:ti,ab OR ambulation:ti,ab

#3 RCT

('clinical trial'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR "latin square" OR 'placebo'/exp OR placebo* OR random* OR 'methodology'/exp OR 'comparative study'/exp OR 'evaluation study'/exp OR 'follow up'/exp OR 'prospective study'/exp OR control OR controll* OR prospectiv* OR volunteer*) NOT ([animals]/lim NOT [humans]/lim)

Embase Session Results (14 Mar 2022)

No.	Query	Results
#7	#6 AND ('article'/it OR 'article in press'/it OR 'review'/it)	**2160**
#6	#3 AND #4 AND [01-07-2007]/sd	**3846**
#5	#3 AND #4	**4868**
#4	('clinical trial'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'clinical trial' OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR 'latin square' OR 'placebo'/exp OR placebo* OR random* OR 'methodology'/exp OR 'comparative study'/exp OR 'evaluation study'/exp OR 'follow up'/exp OR 'prospective study'/exp OR control OR controll* OR prospectiv* OR volunteer*) NOT ([animals]/lim NOT [humans]/lim)	**15349457**
#3	#1 AND #2	**7898**
#2	'exercise'/exp OR 'kinesiotherapy'/exp OR 'mobilization'/exp OR exercis*:ti,ab OR 'physical activ*':ti,ab OR 'physical fitness':ti,ab OR 'walking'/exp OR walk*:ti,ab OR 'running'/exp OR run:ti,ab OR running:ti,ab OR jog:ti,ab OR jogging:ti,ab OR ambulation:ti,ab	**1122683**
#1	'thromboembolism'/de OR 'venous thromboembolism'/de OR 'vein thrombosis'/de OR 'vein insufficiency'/exp OR phlebothrombos*:ti,ab OR 'venous thrombos*':ti,ab OR 'deep vein thrombos*':ti,ab OR 'deep-venous thrombos*':ti,ab OR 'deep-vein thrombos*':ti,ab OR 'postthrombotic syndrome':ti,ab OR 'postthrombosis syndrome':ti,ab OR 'post thrombosis syndrome':ti,ab OR 'post thrombotic syndrome':ti,ab OR 'postthrombophlebitic syndrome':ti,ab OR 'venous stasis syndrome':ti,ab OR dvt:ti,ab OR vte:ti,ab OR 'deep thrombophlebitis':ti,ab OR 'venous insufficien*':ti,ab OR 'insufficient vein':ti,ab OR 'vein insufficien*':ti,ab OR 'venous incompetence':ti,ab OR 'pulmonary embolism*':ti,ab OR 'pulmonary thromboembolism*':ti,ab OR 'postphlebitic syndrome*':ti,ab OR 'postphlebitic disease*':ti,ab OR 'postphlebitic ulcer*':ti,ab OR 'post-phlebitic syndrome*':ti,ab	**252431**

Supplement Table II: Outcomes and questionnaires of Chapter 6 Effect of exercise after a deep venous thrombosis: a systematic review.

Outcomes:

- PTS As defined by the International Society on Thrombosis and Haemostasis (ISTH) (1) a Villalta score of 4 or less indicates the absence of PTS, a score of 5 to 14 indicates mild to moderate PTS, and a score of 15 or more or the presence of a venous ulcer indicates severe PTS, all measured at least 6 months after the DVT (2).
- The Manco-Johnson Instrument is a recommended tool according to the ISTH for standardized PTS assessment and has high validation data in the paediatric population.

Ligament (or muscle) flexibility is defined as the angular rotation of a joint, often the ankle or the knee, using an inclinometer. A larger angel indicates greater flexibility.

Leg volume was measured by the volume of displaced water after placing the lower leg in a container with water.

Leg circumference was measured using a measuring tape and is assessed on different levels of the leg, such as ankle, calf or thigh, depending on the study protocol.

Muscle strength and fatigue was assessed by performing a heel lift test using a standardised cadence tool counting the total number of lifts.

Pain was assessed using a 10 cm visual analogue scale (VAS) score.

Painful calf tenderness was measured with the Lowenberg provocation test. A blood pressure cuff is inflated twice on both the calf of the affected and healthy leg and the value at which the patient perceives pain is scored. The difference between the legs was calculated and the mean value is recoded for follow-up purposes.

The Björgell score was assessed by phlebography. This score divides the deep veins into 14 separate segments. Depending on the extension of the DVT within each segment, a score from 0 to 3 was allocated (0 = no DVT, 1 = less than one-third, 2 = one-third or more but less than two-third, 3 = two-thirds or more of the length of the vein segment), with a maximum of 42 points.

Chronic venous insufficiency (CVI) severity was scored using the Venous Clinical Severity Scores consisting of 10 items, each rated by the examiner from 0-3 (3). An increasing score is associated with more severe CVI.

Calf Ejection Fraction (EF) was measured using air plethysmography. The EF is the ejected calf volume with a single toe raise manoeuvre and is measured by the reduction in volume after tensing the calf muscles. This EF is an indication of the calf pump function and is a reflection of the volume changes by muscular activity.

The Residual Volume Fraction (RVF) was the calf volume that remains after 10 toe raises and was measured by air plethysmography. The RVF reflects the calf pump function during muscular activity and is correlated with ambulatory venous pressure.

Calf muscle strength was assessed by using an ankle isokinetic dynamometer in which the ankle joint was positioned at the rotational axis and ankle motion and isokinetic measurements were performed.

Questionnaires:
The VEINES-QoL measures the venous disease-specific QoL (4). This is a 26-Likert item questionnaire on different domains. A lower score indicates a poorer QoL.

The SF-36 measures generic physical QoL (5). The scales are scored so that a higher score indicates a better health state.

The Aberdeen Varicose Vein survey is used to target patients with venous insufficiency on their QoL and consists of 13 questions with a scoring system ranging from 0 to 100 points (6). The lower the score, the better the QoL is rated.

The CIVIQ questionnaire also focusses on the QoL of patients with venous insufficiently and consists of 20-items exploring different dimensions (7). A low score resembled to better patient comfort.

The Godin Leisure Time Questionnaire measures the habitual physical activity over a typical 7-day period with a continuous outcome, where higher scores indicate increased physical activity (8). Levels of activity can be divided into 3 categories; 0 = no physical activity, 1-20 = mild-moderate active and >20 = highly active.

Paediatric Quality of Life Inventory (PQLI) is a validated questionnaire for measuring health-related QoL intended for children, adolescents and young adults. It has been developed for both healthy individuals as those with an acute or chronic medical condition focussing on four domains: physical, emotional, social and school functioning. A higher score indicates a better QoL.

REFERENCES

1. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost* 2009;7(5):879-883.
2. Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. *Haemostasis*. 1994;24:158a.
3. Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000;31:1307-12
4. Lamping DL, Schroter S, Kurz X, et al. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg*. 2003;37:410–419.
5. McHorney CA, Ware JJE, Raczec AE. The MOS 36-item short form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and health constructs. *Med Care.* 1993;31:247–263.
6. Smith JJ, Garratt AM, Guest M, Greenhalgh RM, Davies AH. Evaluating and improving health-related quality of life in patients with varicose veins. *J Vasc Surg.* 1999 Oct;30(4):710-9.
7. Launois R. Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Quality Life Res* 1996;5:539-54
8. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci.* 1985;10:141–146

Supplementary Table III. Quality assessment of Chapter 6 Effect of exercise after a deep venous thrombosis: a systematic review.

	Junger, 2006 [19]	Blatter, 2003 [20]	Partsch, 2004 [21]	Kahn, 2003 [22]	Shrier, 2005 [23]	Schrier, 2009 [24]	Isma, 2007 [25]	Kahn, 2011 [26]	Padberg, 2004 [27]	Hasan, 2020 [28]
Factor 1: Study aims and design										
1. The rationale/aim of the study is clear.	1	1	1	1	1	1	1	1	1	1
2. The study design is appropriate for the aim of the study.	1	0	0	0	0	0	1	1	1	0
Factor 2: Descriptions of treatment protocol										
3. Description of the disease/condition being treated is adequate	1	0	0	1	1	1	1	0	1	1
4. The rationale for the treatment protocol is clear.	1	1	1	0	1	1	1	1	1	0
5. The treatment protocol (intervention and its duration, outcome measures: quantitative or qualitative, long-term vs. short-term, endpoints) is adequately described.	1	1	1	1	1	1	0	1	1	1
Factor 3: Description of methods and therapeutic/side-effects										
6. Details of methods/procedures are adequate to allow the study to be repeated.	1	1	1	0	1	1	0	1	1	1
7. Therapeutic effects and side-effects are defined.	1	1	1	1	0	0	1	0	1	0
Factor 4: Conduct of the study										
8. Inclusion/exclusion criteria (age range, disease/symptom duration, selection endpoints, diagnosis) are clear.	1	0	0	1	1	1	1	0	1	1
9. The methods of patient recruitment are appropriate.	0	0	0	0	1	1	1	1	0	1
10. Subject assessment was blinded, independent and objective.	1	1	1	1	1	1	0	0	0	0
11. The data collected are relevant and complete.	0	1	0	0	0	0	1	1	1	0
12 Data analysis is appropriate for the design of the study.	1	0	0	1	1	1	0	1	1	1
13. The results for all outcome measures have been clearly reported.	0	0	0	0	0	1	1	0	1	0
Total:	10 (good)	7 (fairly good)	6 (fairly good)	7 (fairly good)	9 (good)	10 (good)	9 (good)	8 (good)	11 (excellent)	7 (fairly good)

Acknowledgements (Dankwoord)

De weg die naar dit proefschrift heeft geleid was er niet één die in een rechte lijn liep. Al een geruime tijd terug ben ik vanwege interesse in wetenschap begonnen met dit onderwerp, nog niet eens zozeer vanwege het onderwerp veneuze insufficiëntie. Naarmate het project vorderde kreeg ik steeds een beter begrip van zowel onderzoek doen als veneuze insufficiëntie op verschillende plekken en via verschillende personen. Gaandeweg heeft een flink aantal mensen mij geholpen en gesteund. Al deze personen wil ik graag bedanken en enkelen wil ik in het bijzonder bedanken.

Allereerst wil ik alle patiënten bedanken die hebben deelgenomen aan de onderzoeken of wier gegevens ik heb mogen gebruiken voor onderzoek. Zonder jullie bijdrage was de totstandkoming van dit boekje niet mogelijk geweest en dankzij deze hulp hebben we de zorg voor patiënten met veneuze insufficiëntie hopelijk wat beter gemaakt.

Mijn promotieteam wil ik bedanken voor de mogelijkheden die jullie mij geboden hebben en de begeleiding tijdens het gehele traject.

Prof. dr. E.M.G.J. de Jong, beste Elke, als mijn promotor heb je mij door de jaren heen veel vertrouwen gegeven in het proces. Je was laagdrempelig beschikbaar wanneer ik met vragen zat waarbij je vervolgens de tijd nam om er, zonder oordelend te zijn, samen uit te komen, ook wanneer je andere belangrijkere zaken aan je hoofd had. Ik heb het als inspirerend ervaren hoe je bepaalde zaken op een begrijpbare, prettige en rustige manier uitlegt. Bedankt voor de manier waarop jij mij met al jouw kennis en ervaring van veel waardevolle adviezen voorzag en voor het vertrouwen dat je mij hebt gegeven.

Mijn copromotoren dr. E.B.M. Kroft en dr. M.J.E. van Tongerlo - van Rijn. Beste Ilse, wat is het alweer een tijd terug dat ik bij jou aanklopte na het verzoek of iemand betrokken wilde zijn bij een onderzoek naar de one-stop clinic in het ZGT in Almelo. Ondanks dat ik destijds geen ervaring had met onderzoek, werd ik geïnspireerd door je enthousiasme en je visie op de zorg voor de patiënt met veneuze aandoeningen. Met jouw expertise en contacten binnen de flebologie heb je mij enorm geholpen met alle onderzoeken. Ondanks je drukke agenda hield je tijd voor de begeleiding en discussies. Bedankt voor je voortdurende vertrouwen en opgewekte en positieve mindset.

Beste Marie Josee, via een omweg kwam ik in een wat later stadium terecht bij jou, maar je hebt een belangrijke rol gespeeld in de kwaliteit van het proefschrift en de kennis die ik heb opgedaan. Je hebt mij op een hoger wetenschappelijker niveau geholpen met leerzame en praktische feedback. Je stimuleerde mij om op verschillende manieren een probleem te belichten en gaf mij ook vrijheid bij de onderzoeken. Enorm bedankt voor je waardevolle samenwerking, je vertrouwen en ook je nuchtere en pragmatische begeleiding.

Graag wil ik de leden van de manuscriptcommissie, prof. dr. D. Ulrich, prof. dr. T.E.C. Nijsten en dr. C.J.M. van der Vleuten hartelijk danken voor het lezen en beoordelen van mijn proefschrift.

Marloes Vermeer, Josien Timmerman en prof. dr. M.M. Vollenbroek-Hutten. Ik wil jullie allen bedanken voor de waardevolle hulp vanuit de ZGT Academie toen ik nog aan het begin stond van mijn wetenschappelijke reis, maar ook daarna waren jullie nog altijd beschikbaar en van waarde. De tips en tricks van dat verzamelen, statistiek en SPSS hebben mij gaandeweg verder geholpen, niet alleen binnen dit promotietraject, maar ook in mijn vervolgopleiding.

Ik wil graag de afdelingen dermatologie en vaatchirurgie van het ZGT ziekenhuis en het Deventer ziekenhuis, het secretariaat dermatologie van het Radboud UMC, de afdeling vaatchirurgie van het Erasmus MC en met name de vaatpoli van het Erasmus MC bedanken voor de ondersteuning en het mogelijk maken om onderzoek te doen op jullie afdeling en met jullie patiënten.

Dr. R.H. Houwing wil ik graag bedanken voor zijn inzet en prettige samenwerking met het Deventer ziekenhuis rondom de onderzoeken naar de uitkomsten van de one-stop clinic opzet.

Thuiszorgorganisaties CarrintReggeland en Zorgaccent wil ik bedanken voor de hulp en bijdragen in de onderzoeken naar de one-stop poli setting. De ondersteuning die jullie hebben geboden is van groot belang geweest om dit onderzoek goed uit te voeren. Meer specifiek wil ik Miriam Wikkerink bedanken. Miriam, bedankt voor je waardevolle hulp en bereidheid om mee te denken over het opzetten van het onderzoek en bijdrage aan het verzamelen van de data.

Beste Miranda en Jennifer, heel veel dank voor jullie geweldige hulp bij het uitvoeren van het onderzoek. Jullie praktische kennis en toewijding hebben een enorme bijdrage geleverd richting het einde van dit project. Ik heb onze

samenwerking altijd als heel prettig ervaren, samenwerking die omlijst was door jullie enthousiasme, humor en bereidheid me te helpen. Bedankt voor de gezelligheid en de koffie na weer de zoveelste lange rit in de trein vanuit het Hoge Noorden naar de Maastad.

Bibi, bedankt voor de nauwkeurige en waardevolle bijdragen aan de onderzoeken. Jouw scherpe blik, oog voor detail en taalgevoel hebben mij geholpen in het opzetten van onderzoek en vervolgens het wetenschappelijk schrijven van artikelen. Enorm bedankt voor je inzet, ideeën en adviezen en je kritische wetenschappelijke blik gedurende het project.

Jaap Koedijk, Ilco Toebes, Nathalie Griffioen en Agnes Looyen, ik wil jullie hartelijk bedanken voor het waardevolle werk dat aan de basis heeft gelegen van dit proefschrift. De opzet en resultaten uit jullie onderzoek vormden een belangrijk vertrekpunt voor mijn eigen onderzoeken en hebben me geholpen dit onderwerp verder te verdiepen en uit te breiden.

Ilse Jansma, ik wil je heel erg bedanken voor je hulp waardevolle bijdrage en deskundigheid en je bereidheid om mee te denken over de onderzoeken.

Graag wil ik ook mijn medeauteurs van alle onderzoeken bedanken voor hun belangrijke bijdrage aan dit proefschrift. Bedankt voor de discussie, constructieve feedback en toewijding aan het wetenschappelijk onderzoek.

Daarbij wil ik al mijn (schoon)familie, vrienden en collega's bedanken voor alle getoonde oprechte interesse.

Lieve huidige en voormalige collega's van de spoedeisende hulp in het ZGT, het MCL/Frisius MC, het UMCG en het Isala. Ik wil jullie allemaal enorm bedanken voor de leuke samenwerking de afgelopen jaren. Het was voor mij altijd erg fijn om te merken wanneer jullie interesse toonden in mijn promotietraject.

Anne, Hamid, Gijs, Koen, Niek, Ronald, Catherine, Michelle, Simone, Pieter, Thea en Anna. Bedankt voor jullie steun tijdens deze rollercoaster van een promotietraject. Van lange avondjes in het ZGT en te laat komen voor het eten aan de P.C. Boutensstraat tot aan de steunbetuigingen in de lange treinrit naar Rotterdam. Bedankt voor alle betrokkenheid, berichtjes en een luisterend oor. Dit is mij heel veel waard geweest.

Mijn vrienden van dispuut 'Funsport', ik ben enorm dankbaar voor de steun, aanmoediging en oprechte interesse die jullie steeds hebben getoond.

Bedankt lieve vrienden van de Pedi Summerschool. De meesten van jullie begonnen tijdens onze leuke commissietijd plots aan een PhD traject waarbij jullie er enorm veel lol in leken te hebben. Misschien is dát voor mij wel hetgeen geweest wat mij over de streep getrokken om er ook voor te gaan. Bedankt voor die stimulans en voor de leuke tijd die ik altijd met jullie heb gehad.

Lieve jaarclub 'Brût', ik wil jullie enorm bedankten voor alle steun en interesse tijdens dit lange traject. Terwijl ik me soms verloor in literatuur en deadlines, hebben jullie me eraan herinnerd dat er een wereld buiten het werk en onderzoek bestaat — een wereld vol humor, vriendschap, wielrennen, eetavondjes en pubquizen. Bedankt voor jullie betrokkenheid en onze waardevolle vriendschap! En kom op Tammo, nog eventjes, ook jij bent er bijna!

Arne en Linda, de afgelopen jaren hebben we niet alleen samen de opleiding tot SEH-arts doorlopen, maar ook veel met elkaar gedeeld — zowel de mooie als de moeilijke momenten, op en buiten het werk. Jullie steun, betrokkenheid en oprechte interesse hebben de intensieve periodes waarin ik aan dit onderzoek werkte een stuk draaglijker gemaakt. Jullie collegialiteit en vriendschap hebben deze reis verlicht, en daarvoor ben ik jullie oprecht dankbaar. Bedankt Linda, dat jij mijn paranimf wilt zijn.

Bart, ik wil je via deze weg ook enorm bedanken voor je hulp gedurende alle jaren. Je oprechte interesse en nieuwsgierigheid, aanstekelijke enthousiasme en onverwoestbare vrolijkheid hebben me meer gesteund dan je misschien zelf beseft. Bedankt voor je tips, je kritische correctiewerk en alle gezellige borrels en etentjes waar we konden sparren en waar ik iedere keer weer frisse moed van kreeg. Ik ben ontzettend dankbaar dat ik je naast een ware vriend, ook mijn paranimf mag noemen.

Mark, Merel, Féline, Juliëtte, Laura en Yannick, bedankt voor jullie betrokkenheid, steun en liefde die ik ontvangen heb van jullie. Bedankt voor de geïnteresseerde vragen en berichtjes de afgelopen jaren.

Lieve mama en papa, ik ben jullie enorm dankbaar voor jullie onophoudelijke steun en oprechte interesse in het onderzoek en mijn opleiding, maar bovenal in mij in het algemeen. Jullie samen belichamen de definitie van onvoorwaardelijke steun.

Jullie staan altijd klaar voor mij en ook voor anderen, zijn altijd nieuwsgierig naar hoe het gaat en verwachten er bovenal nooit iets van terug. Bedankt voor al jullie wijze levenslessen en jullie onuitputtelijke liefde.

Lieve Femke, wat heb je vele uren moeten doorbrengen waarbij ik weer diep in de materie en de laptop verzonken zat. Jij bent gedurende dit hele traject mijn grote steun geweest en tot aan de laatste correcties stond je naast me met ontelbare kopjes koffie, maar bovenal eindeloos geduld, begrip en liefde. Je luisterde naar mijn verhalen over data, analyses en deadlines, ook als ze eindeloos leken te duren. Mede dankzij jouw vertrouwen, rust en aanstekelijke optimisme kon ik steeds weer de energie vinden om door te gaan. Je stond altijd klaar, zonder iets terug te verlangen en dat heeft meer voor mij betekend dan ik ooit goed kan uitdrukken.

About the author (Curriculum Vitae)

Bram Rook werd als middelste van drie kinderen geboren op 9 december 1992 te Zwolle. Hij groeide op in Sint Jansklooster. Zijn VWO diploma heeft hij gehaald aan het Meander College in Zwolle in 2011. Datzelfde jaar werd hij middels de decentrale selectie geplaatst voor de studie geneeskunde in Groningen. Naast zijn studie heeft hij zich actief ingezet bij zijn studie als student-assistent, zijn studievereniging M.F.V. Panacea en bij de studentenvereniging A.S.V. Dizkartes. Zijn bachelor geneeskunde rondde hij in 2014 af, waarna hij zijn coschappen in het ZGT in Almelo en Hengelo deed. Tijdens deze periode is hij begonnen met wetenschappelijk onderzoek onder leiding van dr. E.B.M. Kroft, dat de basis heeft gevormd van zijn proefschrift. Deze periode rondde hij af met een keuzecoschap in het Dodoma Regional Referral Hospital in Dodoma, Tanzania. Zijn semi-arts stage en masteronderzoek heeft hij verricht op de afdelingen gynaecologie in respectievelijk het Isala ziekenhuis in Zwolle en het Universitair Medisch Centrum (UMCG) in Groningen, waarna hij zijn artsenbul behaalde in 2018. Vervolgens heeft hij achtereenvolgens anderhalf jaar op de spoedeisende hulp in het ZGT te Almelo en op de spoedeisende hulp van het Medisch Centrum Leeuwarden gewerkt als arts-assistent. In 2021 is hij begonnen met de opleiding tot Spoedeisende Hulp arts in het Medisch Centrum Leeuwarden en het UMCG te Groningen welke hij afrondde met een keuzestage in het Khayelitsha Hospital te Kaapstad, Zuid-Afrika.

Onder leiding van prof. dr. E.M.G.J. de Jong en zijn copromotoren Dr. E.B.M. Kroft en Dr. M.J.E. van Tongerlo - van Rijn heeft hij sinds 2015 naast zijn studie geneeskunde en opleiding tot SEH-arts gewerkt aan wetenschappelijke onderzoek in het ZGT te Almelo, het Deventer Ziekenhuis, het Medisch Centrum Leeuwarden en het Erasmus Medisch Centrum te Rotterdam. In 2020 is hij officieel begonnen met zijn promotietraject aan de Radboud Universiteit te Nijmegen als buitenpromovendus.

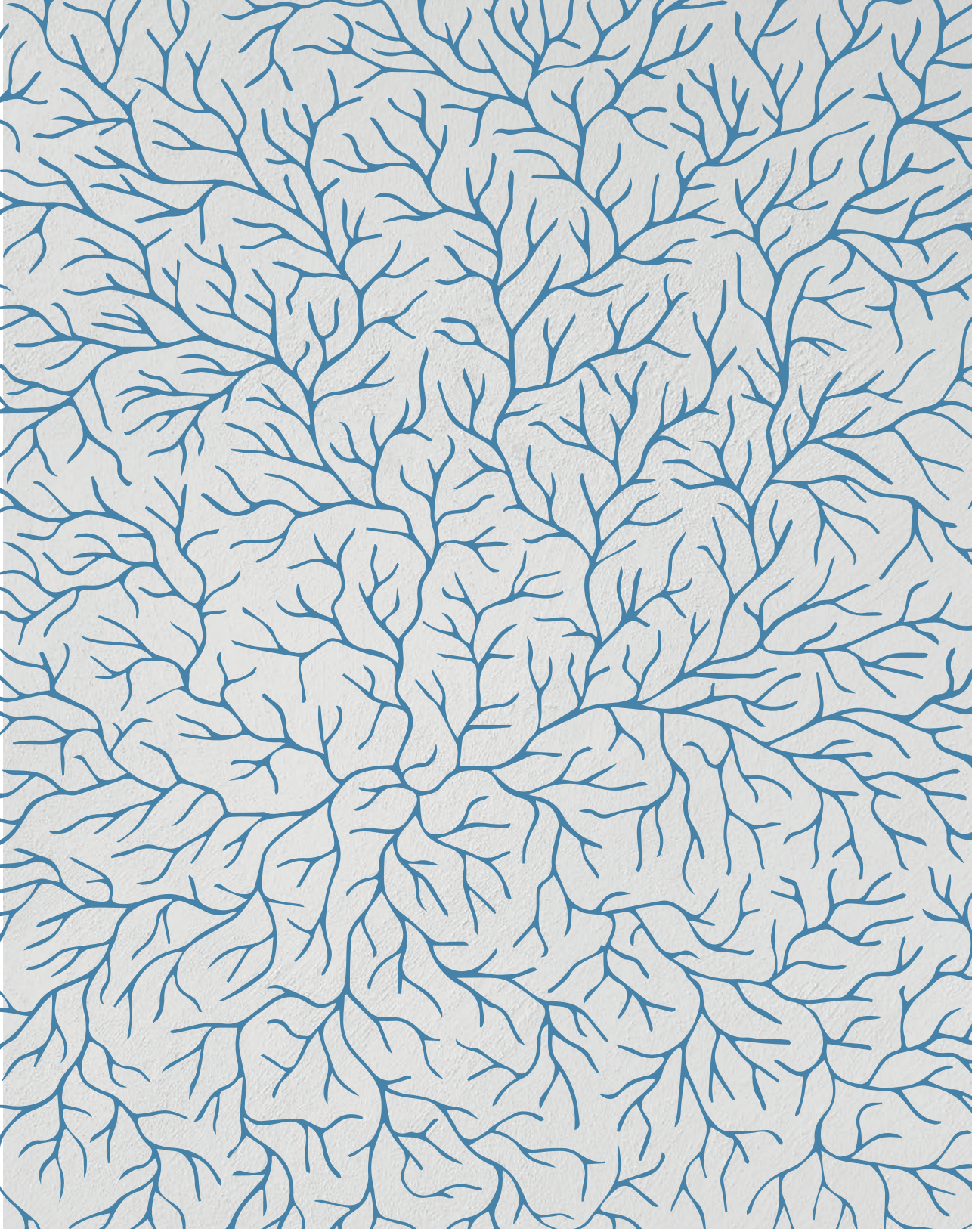
Sinds 10 november 2024 is hij geregistreerd SEH-arts en is hij met veel plezier werkzaam als fellow in het Isala Ziekenhuis in Zwolle en het Frisius Medisch Centrum in Leeuwarden.

Portfolio

PhD portfolio of Bram Rook

Department: **Dermatology Department, external PhD candidate.**
PhD period: **01/02/2020 – 31/12/2025**
PhD Supervisor: **Prof. dr. E.M.G.J. de Jong**
PhD Co-supervisor(s): **Dr. E.B.M. Kroft – Bult, Dr. M.J. van Tongerlo - van Rijn**

Training activities	Hours
Courses	
• Radboudumc - Scientific integrity (2023)	20.00
• GCP-WMO re-registration (2023)	16.00
• Regionaal Opleidingsprofiel 'Management & Bestuur' voor aios (2024)	81.00
• ICH GCP R3 Certificate Update Training addendum to valid BROK/GCP Certificate (2025)	8.00
Conferences	
• Into Veins congres 2022 (2022)	16.00
Teaching activities	
Total	**141.00**



Radboudumc
university medical center

IN DEI NOMINE FELICITER

Radboud University