Treatment and Quality of Life of Patients with Varicose Veins

Anke A.M. Biemans

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bij patiënten met varices

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LIST OF FREQUENTLY USED ABBREVIATIONS

AASV, anterior accessory saphenous vein
ASVAL, ambulatory selective varicose ablation under local anesthesia
AVVQ, Aberdeen Varicose Vein Questionnaire
CEAP, Clinical Etiology Anatomy Pathophysiology classification
CIVIQ, Chronic Veines Insufficiency Quality of Life Questionnaire
CS, conventional surgery (ligation with stripping)
CVD, chronic venous disorder
CVI, chronic venous insufficiency
DUS, duplex ultrasound
DVT, deep vein thrombosis
EQ5D, EuroQoL 5D
EVLA, endovenous laser ablation
EVTA, endovenous thermal ablation
GSV, great saphenous vein
HRQoL, health related quality of life
LMWH, low molecular weight heparin
PRO, patient reported outcome
RCT, randomized controlled trial
RFA, radiofrequency ablation
SF-36, Short Form 36
SFJ, saphenofemoral junction
SPJ, saphenopopliteal junction
SSV, small saphenous vein
UGFS, ultrasound guided foam sclerotherapy
US, ultrasound examination
VCSS, venous clinical severity score
VEINES, VEnous INsufficiency Epidemiological and Economic Studies

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Chapter 1

General Introduction

GENERAL INTRODUCTION

Chronic venous disorders (CVD) are defined as *the full spectrum of morphological and functional abnormalities of the venous system,* from telangiectasia to venous ulceration. Different forms of CVD may have a great impact on patients' quality of life and therefore CVD represents an important social as well as economic burden. The incidence of CVD increases with age, except for congenital venous malformations.

CVD may start with minor symptoms and/or appearance of varicose veins. Long-standing CVD may slowly progress over time, leading to oedema and skin changes such as pigmentation, "atrophy blanche" (white atrophy), lipodermatosclerosis and finally leg ulceration. Chronic venous insufficiency (CVI) is a part of CVD where the function of the venous system is disturbed and leads to clinical complications. These more advanced stages are classified in the CEAP classification as C3 to C6 (see page 15). Other clinical manifestations of advanced CVD are varicose veins, blow outs, nail changes, subcutaneous calcifications, induration, pachyderma and eczema.

PHYSIOLOGY AND PATHOPHYSIOLOGY

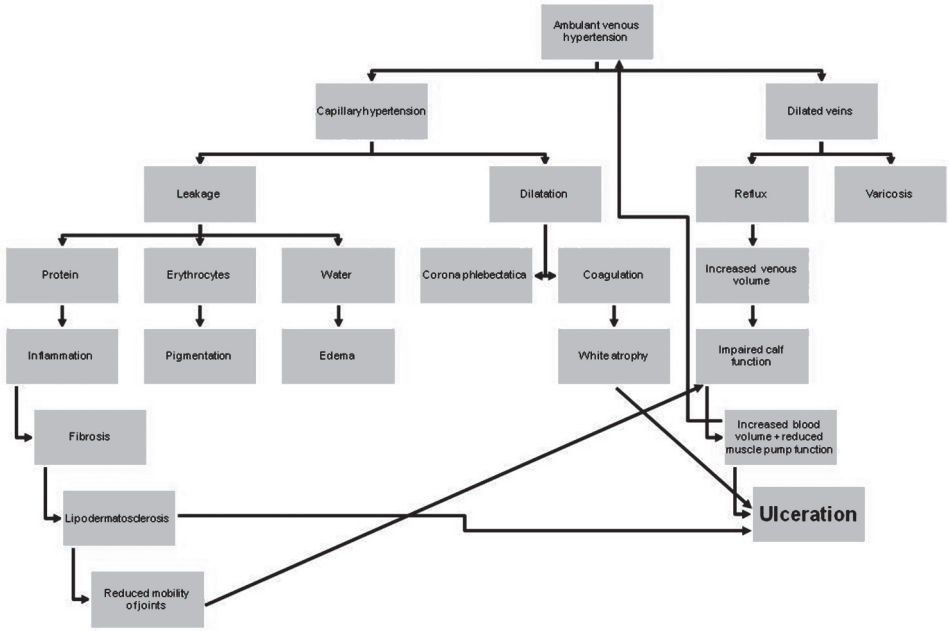
Veins return the deoxygenated blood from the tissues to the heart. In the upright position, especially when standing still, gravitation has to be overcome, to ensure venous flow. Among different mechanisms for the venous return, the muscle pump function is the most important. Deep intramuscular veins are being compressed during muscle contraction. In addition, valves play a major role in maintaining the right flow direction, from the extremities towards the heart. After compression of the muscle the blood flows though the perforator veins to the deep system. The most important pump in the lower extremity is the calf muscle pump, followed by the compression of the plantar plexus during walking.

In standing position, with open valves, the pressure in the veins is around 90 mmHg. After activation of the muscle pumps this pressure decreases to 20 mmHg. However, when there is valve incompetence or severe venous insufficiency, due to deep venous thrombosis, the pressure will decrease less. This condition is called increased ambulant venous pressure or venous hypertension.[1,2] The high venous pressure will be transferred, to the venular side of the skin microcirculation.[3,4] Capillary hypertension causes capillary leakage of fluid which is responsible for oedema, and erythrocytes migrating from the capillaries leading to iron deposition and -hyper pigmentation.[5] Leakage of plasmaproteines induces an inflammatory reaction resulting in lipodermatosclerosis.[3,6] Capillary hypertension also leads to dilation of capillaries that cause decrease of the blood flow velocity with deposition of fibrin and thrombocytes and leukocyte adhesion, leading to microthombosis, with atrophy blanche as a result. [7, 8] These skin changes lead to skin that is vulnerable to venous ulcerations.[4] (Figure 1)

The pathogenesis of primary venous reflux and the etiologic mechanism of morphologic changes in the vein wall are largely unknown. For a long period the hypothesis was that varicose veins develop due to inborn unstable elastic layer in the vein wall and that widening takes

place mainly under influence of gravitation.[9,10] The increase of vein diameter makes the valves incompetent (leakage) and this results in reflux. There are two possibly etiologic explanations. In the first concept varicose dilation will develop first in the cranial part of a vein and extend distally along with the effect of gravitation, progressively affecting the more distal valves (descending varicosity, Figure 2a).[11-13] Contrarily, there is increasing evidence that superficial venous disease has a multifocal origin and can be 'ascending' from the tributaries towards the saphenous trunk, and further to the junction.[11,14-19] Other studies also found evidence for the ascending concept (Figure 2b) with disappearance of GSV reflux after phlebectomy or ablation of an incompetent tributary, as well as the reduction in GSV diameter after ablation of refluxing collaterals.[19-23] Probably both theories play a role in the etiology of varicose veins.

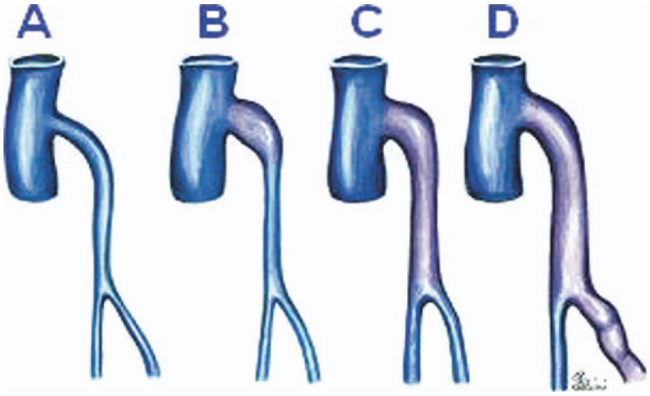
Figure 1: Rotterdam Model of CVD.



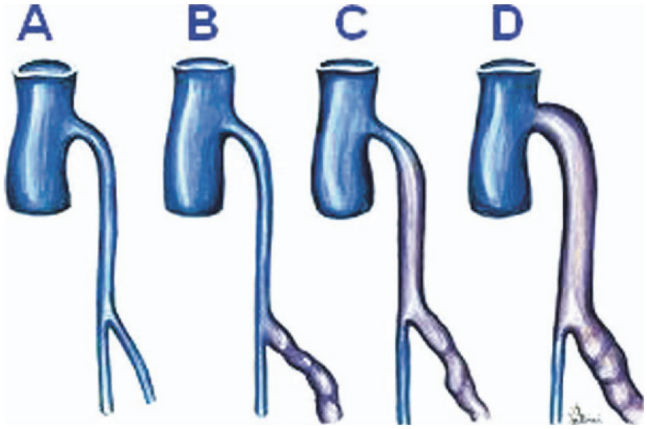
EPIDEMIOLOGY

There is a lot of epidemiological data about CVD available in the literature.[24-27] CVD is not only a European problem. It affects a significant part of the population worldwide. Recently the findings of the Vein Consult Program, an international observational, prospective study collecting global epidemiologic data on chronic venous disorders, based on the CEAP classification (Table 1, tekst page 15), have been published. In a total cohort of 91545 adults, the world wide prevalence of these disorders was 83.6% (19.7% subjects with C0 and 63.9% with C1-C6 according to the CEAP classification.[28]

Figure 2: Descending and ascending theory.



2a. Progression of varicose changes (from A to D) according to the descending theory.



2b. Progression of varicose changes (from A tot D) according to the ascending theory.

Varicose veins are a common manifestation of CVD. General population studies reported a prevalence of varicose veins in 10-40% in men and 26-32% in women.[24,29-31] The incidence of varicose veins increases with age in a linear manner. The overall prevalence of saphenous varicose veins in the Edinburgh Vein Study, which is a general population study, increased from 12% in those aged 18-24 years to 56% in those aged 55-64 years.[24] These findings are concordant with the Framingham Study results in which the prevalence of varicose veins in women younger than 30 years was less than 10% while in women aged 70 years and older it increased to 77%.[32] Multiple studies have shown that varicose veins are more common in

women than in men. Selection bias may be a problem, as women consider varicose veins more often a cosmetic problem than men, present more frequently at a varicose vein clinic and are therefore more likely to participate in studies. Most general population studies could not demonstrate a sex difference. Moreover, more advanced CVD occurs equally in both sexes.[33] It is estimated that venous leg ulceration, the end stage of CVI, affects 1% of the population.[34] It is assumed that approximately 50% of venous leg ulcers are the result of superficial varicose veins.[35] Therefore, the treatment of varicose veins, which may reduce the incidence of leg ulcers by 50%, is likely to be cost-effective. The prevalence of venous ulcerations decreases slightly the last years. Possibly this is due to early and more effective treatments of venous disorders. (2.7% in 1970[30] en 0.6% in the Edinburgh Vein Study[24] en 0.7% in the Bonn Vein Study I.[33,36]

CLINICAL CHARACTERISTICS

CVD is associated with multiple and generally subjective symptoms consisting of discomfort, aching, tingling, heaviness, burning, itching, muscle cramps and leg tiredness. The clinical characteristics of CVD appear when the mechanisms that compensate for insufficient venous return fails. The clinical features increase almost linearly in time and consist of teleangiectasias, varicose veins, oedema, hyperpigmentation, eczema, atrophy blanche, lipodermatosclerosis and ulceration. (Figure 3)

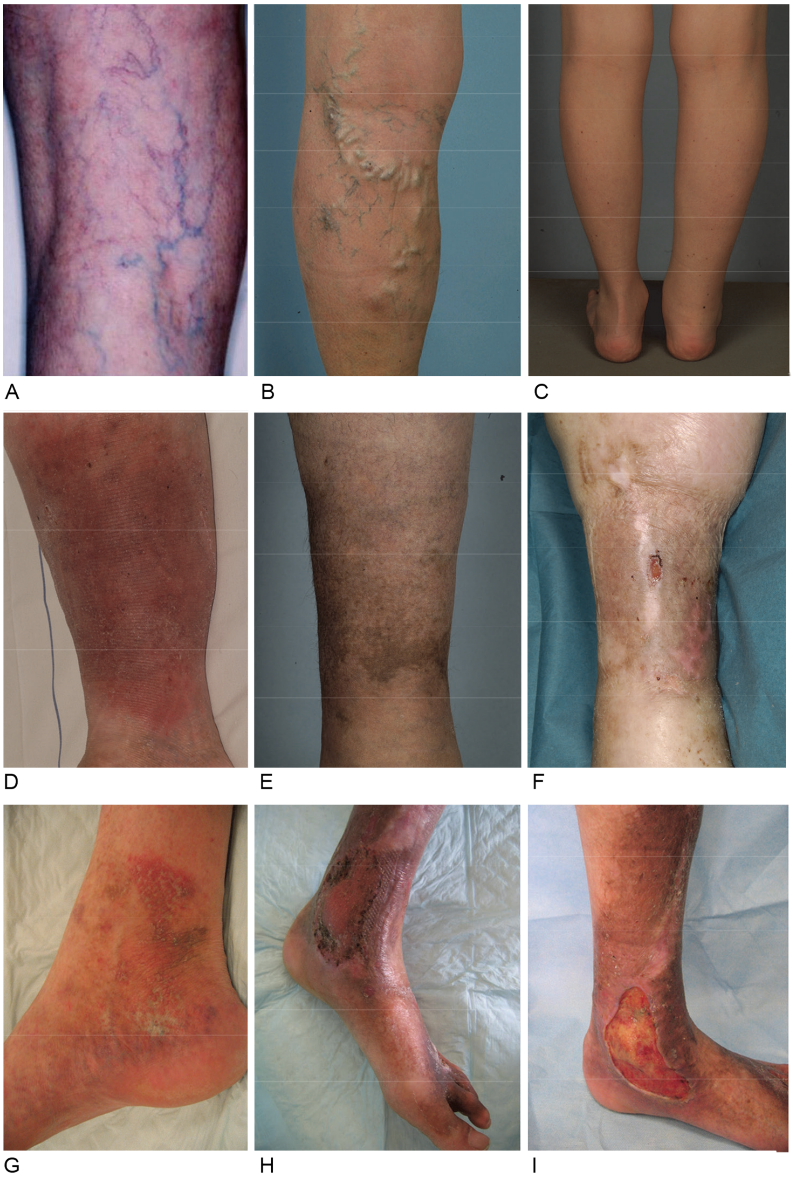
The CEAP classification (Table I) has been described to classify patients with CVD based on clinical characteristics and duplex ultrasound findings.[37,38] The CEAP classification is used for the description of Clinical signs of CVD, Etiology (congenital, primary or secondary), Anatomy (superficial, deep and perforating veins) and Pathophysiologic (reflux, obstruction or both). The CEAP classification serves as an orderly documentation system and forms a synthesis of the phlebological status. Eklöf et al. revised and refined the original classification, also introducing the nowadays most frequently used basic CEAP as a simpler alternative to the advanced CEAP classification.[37]

Diagnostics

At the end of the last century duplex ultrasound (a combined use of echography and Doppler) has been widely introduced as diagnostic tool for CVD, and has now replaced many of the previously available tests. Duplex ultrasound (DUS) allows detailed visualization of the anatomy (veins, arteries, nerves, muscles etc) and provides all useful information about blood flow hemodynamics. Duration of reflux time, peak reflux velocity and other parameters can be measured by means of pulsed wave Doppler technology. Flow direction can also be visualized directly by using colour coding technology, which is integrated in all modern duplex devices. Reflux in superficial veins is defined as duration of reverse flow during >0.5 s. In addition the diameter of the vein can be measured. Duplex ultrasound is now the gold standard diagnostic technique,[39] which should be available in each phlebologic practice. Excellent guidelines have

been published, which are helpful to unravel the duplex anatomy[40] in patients presenting with varicose veins and other venous disorders, as well as to investigate the veins after treatment. [41]

Figure 3: Clinical characteristics of chronic venous disorders.



A. Telangiectases and reticular veins; B. Varicose veins; C. Edema (right leg); D. Eczema; E. Hyper pigmentations; F. Lipodermatosclerosis (with small ulcer pretibial); G. Atrophy blanche; H. Healed ulcer; I. Active ulcer

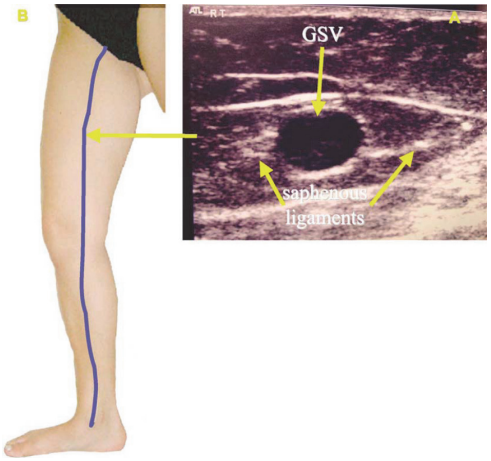
Table I: Revision of CEAP Classification of chronic venous disease: summary.[37]

Clinical classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasies or reticular veins
C_2	Varicose veins
C_3	Edema
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Etiologic classification	
Ec	Congenital
Ep	Primary
Es	Secondary (postthrombotic)
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
Basic CEAP	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable
Advanced CEAP	
Same as basic CEAP, with addition that any of 18 named venous segments can be used as locators for venous pathology.	

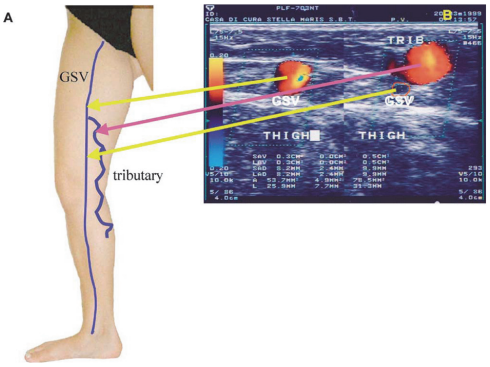
DUS has largely contributed to clarify venous anatomy. For instance the saphenous compartment in which the saphenous trunks run. In a transverse scan this compartment resembles an, 'Egyptian eye'. (Figure 4a) The 'eye' sign is always present and allows clear identification of the saphenous vein. In this way, the main trunk of the great saphenous vein

(GSV), small saphenous vein (SSV), anterior accessory saphenous vein (AASV) and posterior accessory saphenous vein (PASV) can be clearly distinguished from tributaries running in the subcutaneous tissue, outside the saphenous compartment. (Figure 4b) Knowledge of the anatomy of this compartment is also essential when performing all types of endovenous procedures. Before ablation tumescent anaesthesia is injected, exactly in the saphenous compartment, under ultrasound guidance.

Figure 4: Duplex ultrasound characteristics.



4a: Transverse ultrasound image of the great saphenous vein (GSV) in the saphenous compartment of the thigh. Cavezzi, Eur J Vasc Endovasc Surg 2006;31:288-299. Copyright 2006 Elsevier Inc. All rights reserved.



4b: Relationship between the great saphenous vein and a tributary in the mid thigh area (**A**) diagram showing the position of the GSV and of its (incompetent) tributary. (**B**) transverse colour duplex image: Left: GSV within the saphous eye. Right: tributary above the saphenous fascia and GSV with the saphenous eye (right). Cavezzi, Eur J Vasc Endovasc Surg 2006;31:288-299. Copyright 2006 Elsevier Inc. All rights reserved.

DUS is also the ideal non-invasive method for follow-up after treatment, as it provides anatomical and hemodynamic information about the treated veins.[41] DUS can detect the early stages of recurrent varicose veins before they become apparent clinically.[42] Serial DUS imaging can not only help to understand the clinical evolution of the individual patient after treatment for CVD, but also has the potential to increase the general knowledge of events leading to clinical recurrence. Thus, long-term follow-up using DUS extends the understanding of the natural evolution of varicose vein disease.[41]

A potential disadvantage of duplex ultrasound is the fact that it is strongly operator dependent and hence there is a considerable risk of over-, or underestimation or even complete misinterpretation. Intensive training is therefore essential for all those who want to be involved in phlebology and treat patients with venous problems.

In addition to duplex ultrasound, other, more sophisticated investigations may be indicated in patients with complex hemodynamic problems. Phlebography, CT- or MR-venography, ambulatory venous pressure measurements and plethysmography can all be used for additional assessment. In particular when clinical signs are not corresponding with duplex ultrasound findings or in view of planning interventional treatment, extensive further investigation will be warranted.

ADDITIONAL ASSESSMENTS

In addition to the initial clinical classification by means of the 'C' of the CEAP classification a clinical scoring system has been developed in 2000[43] and revised in 2010,[44] the Venous Clinical Severity Score (VCSS), which results in a more quantitative evaluation of the disease (Table II). As it evaluates different features of venous disease that may change after treatment it facilitates evaluation during follow-up and is therefore often used in clinical trials.

Another important issue is the evaluation of the patient's quality of life. For centuries evaluation of medical treatment has mainly focused on outcome parameters directly related to the treatment itself. Presence (or absence) of clinical recurrence and of reflux have been used as the only parameters for evaluation of varicose treatment. How the disease affected the patient's quality of life and whether treatment had improved this was rarely taken into account. Nowadays more and more researchers incorporate health related quality of life (HRQoL) as an important outcome parameter in clinical trials. Also in phlebology quality of life is an important issue.[45] As general questionnaires for measuring HRQoL have no questions related to phlebological problems several disease specific questionnaires have been developed the last years.

In phlebology, the most commonly used generic instruments are the Short Form 36 (SF-36) and the EuroQol (EQ)-5D. Since these measures were developed to be used across many different diseases, they lose accuracy in diseases with specific HRQoL impairment, such as varicose veins. For this reason disease specific instruments are now increasingly used to

Table II: Revised Venous Clinical Severity Score.[44]

	None: 0	Mild: 1	Moderate: 2	Severe: 3
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin		Occasional pain or other discomfort (ie, not restricting regular daily activities)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)
Varicose veins "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position.		Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Confined to calf and thigh
Venous edema Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or Focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 months	>3 months but <1 year	Not health for >1 year
Active ulcer size (largest active)	N/A	Diameter <2cm	Diameter 2-6 cm	Diameter >6cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

evaluate the effects of specific treatments in patients with varicose veins, in combination with generic instruments.[46-49] The available disease specific HRQoL tools focusing on chronic venous insufficiency and/or varicose veins are: Chronic Lower Limb venous Insufficiency (CIVIQ), Aberdeen Varicose Vein Questionnaire (AVVQ) and VEINES-QOL/Sym.[47-49] The CIVIQ focuses on HRQoL impairment and includes only one symptom related item. The CIVIQ results in a global score and four separate domain scores (physical, psychological, social impairments and level of pain)[47]. The AVVQ calculates one global HRQoL score summing symptom and clinical class related items.[48] The VEnous INsufficiency Epidemiological and Economic Studies (VEINES) questionnaire is positioned in between these two instruments because it balances symptom (VEINES-SYM) and quality of life (VEINES-QOL) items resulting in two separate scores.[49]

Most of these questionnaires do not exist in the mother tongue of the patients. For use in the Netherlands these questionnaires should be translated to Dutch and validated.

Although there are neither guidelines nor any evidence that this HRQoL investigation has to be done in every patient undergoing treatment, it may be helpful to evaluate different techniques and to determine optimal treatment strategies.

TREATMENT

There are three main reasons to treat patients with varicose veins. First of all, treatment aims at preventing acute complications, such as bleeding and superficial vein thrombosis and chronic deterioration consisting of all clinical features of chronic venous insufficiency (C3-C6). All these have a major impact on patients' HRQoL. Secondly, treatment relieves symptoms caused by varicose veins, such as heaviness, tired legs, cramps etc. Thirdly, patients may seek for treatment mainly for cosmetic reasons which also affect patient's HRQoL.

Treatment of varicose veins can roughly be divided into four groups: compression therapy, endovenous thermal ablation, sclerotherapy and surgical treatment. In this thesis only treatment of the great saphenous vein (GSV) and tributaries will be considered.

Treatment of the GSV

In 1905 Keller described a surgical technique to remove the GSV by stripping and invagination.[50] For nearly 100 years high ligation and stripping was the gold standard for the treatment of incompetence of the GSV.

Although sclerotherapy had already been introduced in the mid 19th century this technique was reintroduced after the Second World War.[51] It gained more and more interest when a technique was developed to make foam with the detergent sclerosing agents.[52-54] Nowadays the Tessari method is widely accepted for routine foam sclerotherapy of refluxing saphenous trunks and tributaries.[55]

The true 'endovenous revolution' started with the beginning of the 3rd millennium. Endovenous thermal ablation (EVTA) techniques were introduced. The first EVTA procedures

were performed with radiofrequency ablation (RFA) with the VNUS Closure Plus System.[56] Immediately thereafter endovenous laser ablation (EVLA) was developed. The radiologist Min introduced a minimally invasive endovenous laser treatment for varicose veins, aiming at elimination of incompetence at the saphenofemoral junction (SFJ) and closure of the GSV.[57,58] The first ELVA procedures were with 810nm diode laser, of which hemoglobin is the main target. Laser light absorption is followed by heat production. This heat is transmitted to the vein wall leading to destruction. The precise mechanisms of EVTA and the relation with wavelength, chromophores and carbonization are not yet completely understood. A meta-analysis showed that the above described minimally invasive techniques appeared to be at least as effective as surgery for the treatment of varicose veins.[59]

Nowadays EVLA has turned into a generally accepted, easy to perform and patient friendly technique.[60] The actual tendency is to use lasers with higher wavelengths up to 1470nm[61] and to move to modified laser tips such as the radial tip, tulip-tip and others replacing the initial bare tip laserfibers. The newest thermal technique is steam ablation, which works by heating the vein wall with hyperheated steam.[62]

Treatment failure and varicose vein recurrence remains a problem occurring after all treatment modalities. Different etiologic factors may play a role in the development of recurrence: tactical and technical failure, neovascularisation (mainly after surgery, at the site of high ligation), recanalisation of a previously obliterated trunk (after endovenous ablation) and finally, progression of the disease. Prevention of recurrence should try to interfere with these factors. In the first place, a thoroughly performed duplex ultrasound should lead to a correct diagnosis of the varicose disease, to avoid tactical failure. Further, the planned procedure should be performed correctly. Training in duplex scanning and in ultrasound guided procedures is therefore the cornerstone of good clinical practice in phlebology. Neovascularisation, mainly at SFJ and saphenopopliteal junction (SPJ) remains a concern after surgical treatment of varicose veins. It can be easily detected by means of duplex ultrasound, which shows the presence of multiple tortuous veins at the site of the previous high ligation or in the strip track.[41] Some barrier techniques to mitigate the effect of neovascularisation at the SFJ or SPJ have been tried out successfully.[63,64] However, the best way to avoid neovascularisation seems to be not to operate at the SFJ or SPJ. Nowadays, in many countries like the Netherlands, surgical high ligation and stripping has been replaced by endovenous ablation techniques. After these endovenous interventions indeed neovascularisation is a very exceptional phenomenon. However recurrence remains a problem, also after endovenous techniques. It may be due to recanalisation of the obliterated trunk, with or without recurrent reflux at the junction. Prevention of recanalisation after thermal ablation is mainly a matter of using enough tumescence and a correct amount of energy, dependent of vein diameter. The only factor we cannot really influence, unfortunately, is progression of the disease. To further unravel the problem of recurrent varicose veins after all kinds of interventions for varicose

veins, more and better performed randomized studies with long-term follow-up (of at least 5 years) are certainly needed.

Treatment of tributaries

Pittaluga showed that incompetent tributaries may render the GSV incompetence, based on the ascending pathophysiologic theory. Under certain circumstances single treatment of such incompetent tributaries – without treatment of the refluxing GSV trunk – may abolish truncal reflux completely. If this is the case, unnecessary ablation of a refluxing trunk could be avoided in certain cases. Properly selected patients could benefit from a treatment of refluxing tributaries only. This finding certainly needs more research.

The gold standard for treating incompetent tributaries is ambulatory phlebectomy, based on the findings of a randomised controlled trial comparing liquid sclerotherapy with phlebectomies for tributary treatment.[65] So far no randomised controlled trial is available in which foam sclerotherapy and ambulatory phlebectomy are compared.

Research in medicine is done to improve the quality of diagnosis and treatment. The translation from pure research to daily practice is the aim of every clinical investigator. In the last two decades translation of evidence based research has changed phlebological practice considerably. Duplex ultrasound has become the gold standard for diagnosis and treatment guidance. Major surgery has largely been abandoned and more patient friendly, less expensive and minimally invasive endovenous techniques and surgical procedures have been introduced. Diagnosis and treatment of CVD, and especially of varicose veins, can be realised in nearly 100% in day care, often in special clinics dedicated to phlebology. Compared to the situation 25 years ago, there is now growing interest in integrating HRQoL investigation in our clinical research. Not only will the individual patient benefit from this, but also society as a whole, as it may lead to more responsible choices in treatment strategy for patients with varicose veins.

AIMS OF THE THESIS

To contribute to evidence-based medicine and identify gaps in the knowledge concerning the treatment of saphenous varicose veins we performed a systematic literature research. (Chapter 2).

There are a few questionnaires available to assess patient reported outcome or HRQoL, but so far only one of these questionnaires was available in Dutch. Patient reported outcome instruments are necessary to answer several questions in scientific investigations. We therefore translated and validated the CIVIQ and the VEINES Sym/QoI for Dutch patients with varicose veins. (Chapter 3)

The third aim was to investigate the best treatment options for patients with GSV incompetence. In a randomized controlled trial we evaluated the effect of three commonly used treatment methods for insufficiency of the GSV; endovenous laser ablation, ultrasound-guided foam sclerotherapy and conventional surgery. (Chapter 4) In a subsequent prospective study we wanted to evaluate the effect of single phlebectomies on the reflux of the GSV and to describe predictors for success of this approach. (Chapter 5) After a literature search we reviewed the existing evidence on recurrence after different treatment techniques. (Chapter 6)

In summary, first we tried to comprehend the current literature on varicose vein treatments, and find evidence for what could be the most successful therapy with the least complications. Then we translated and validated two disease specific HRQoL questionnaires, that can be used in future studies. In a randomized controlled trial we compared the three most used treatments for GSV incompetence. We further evaluated the effect of phlebectomy of tributaries on GSV reflux and made a prediction model by means of a score chart. Finally, we reviewed the literature on the subject of recurrent varicose veins after treatment. In the discussion we highlighted the importance of the patients' voice, which might be more important than clinical recurrence and duplex ultrasound results. The studies in this thesis will contribute to the translations of our findings to a more rational treatment approach in daily practice fore varicose patients.

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Chapter 2

Endovenous Therapies of Varicose Veins: Indications, Procedures, Efficacy and Safety

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ABSTRACT

Venous insufficiency of the lower-extremity is common and the prevalence increases with age. Chronic venous insufficiency has a high impact on patients' health related quality of life and is associated with considerable health care costs. In addition to classical symptoms, it may result in skin changes and venous ulcers. Since more than hundred years, surgical ligation of the junction with or without stripping has been the standard of care in the treatment of insufficient great and small saphenous veins. However, the recurrence rates are relatively high and surgery may be associated with serious adverse events, considerable down time and is cosmetically suboptimal. In the last decade several minimally invasive techniques have been introduced, to improve efficacy, patients' health related quality of life and treatment satisfaction, and to reduce serious side effects, costs and post-operative pain. Ultrasound guided foam sclerotherapy, endovenous laser and radiofrequency ablation are the most commonly used therapies, and challenge surgery as the gold standard of care in patients with varicose veins. The objective of this review is to inform clinicians about these three therapeutic options for saphenous varicose veins and to describe and compare the indications, procedures, efficacy and safety profile.

INTRODUCTION

Symptomatic varicose veins of the lower extremities represent one of the most common conditions in the adult population. About 25% of the population has lower-extremity varicose veins[1] and half of the adult population has stigmata of minor venous disease.[2] Since the prevalence of varicose veins increases with age in a linear manner, the prevalence of venous insufficiency will increase considerably in the next decades. Associated symptoms range from mild complaints such as fatigue, heaviness, and itching to more serious conditions such as edema, skin hyperpigmentation, eczema and leg ulceration. Venous ulcers have a prevalence of 1-2% in people over 65 years of age.[3] Chronic venous insufficiency has, because of its complications, a great impact on patients' health related quality of life (HRQoL), and it is associated with considerable health care costs.[4] In the Netherlands, chronic venous insufficiency and its related venous ulcers, costs approximately 1% of the national health care budget. It has been estimated that about half the venous ulcers can be prevented by treating the varicose veins.

The mean goal in the treatment of varicose veins is to reduce the symptoms and complications of chronic venous insufficiency, and to improve health-related quality of life (HRQoL) of patients. Surgery has been the standard of care in the treatment of saphenous varicose veins for more than a century. More than a quarter of all cases of chronic venous insufficiency is caused by reflux of the great saphenous vein (GSV), and is traditionally treated with surgical ligation at the saphenofemoral junction and stripping of the incompetent saphenous vein. Usually, surgery of the small saphenous vein (SSV) consists of ligation at the saphenopopliteal junction (SPJ) with or without a short strip until the mid-calf of the SSV. It is well-known that stripping is related to a high recurrence rate and neovascularization. The recurrence rate of surgery is about 25% for the GSV and 50% for the SSV after 5 years.[5] After a mean follow-up of 34 years, Fischer showed a recurrence of varicose veins in 60% in 125 limbs after SFJ ligation and GSV stripping.[6] Neovascularization, a double saphenous vein system, technical failure (up to 30%)[7] and/or incomplete procedure[5,8] are several reasons of failure after surgery. Other disadvantages of surgical therapy are the common use of general or epidural anesthesia, presence of at least two fairly-long scars, post-operative down time and risk of adverse events such as femoral artery or femoral vein damage, wound infection, neurological injury (about 7% in short to 40% in long stripping of GSV)[9] and lymphatic complications. New minimally invasive techniques such as ultrasound guided foam sclerotherapy (UGFS), endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) have been introduced in the last decade, to improve the efficacy, patients' HRQoL and treatment satisfaction, and to reduce serious side effects, costs and post-operative pain.[10] These new methods can be performed in outpatient settings or ambulant day-care facilities. This has an additional advantage compared to surgery, which is usually performed in the operating theatre under general or spinal anesthesia. Dermatologic surgeons were among the first in developing and

reporting on these minimal invasive techniques for saphenous varicose veins such as RFA, EVLA and UGFS. The objective of this review is to inform physicians about the most commonly used minimal invasive therapies used for saphenous varicose veins, to describe the procedures and to review their efficacy and safety.

ULTRASOUND GUIDED FOAM SCLEROTHERAPY (UGFS)

The use of foamed sclerosants has been described since 1944, when Orbach injected a small amount of air into the venous segment targeted for treatment in order to displace blood and intensify the contact time between sclerosant and the endothelium of the vein (so called, 'air block' technique).[11] Liquid sclerotherapy is an established method of causing venous occlusion by the injection of sclerosing liquid into affected veins. Direct contact of sclerosant with the venous endothelium initiates endothelial and mural injury by an irritative reaction. As a result, a local, wall-adherent thrombus is formed and subsequent sclerosis transforms the treated vein into a fibrous cord.[12,13] The success of foam, which is more effective for the treatment of saphenous veins than liquid, is mostly caused by its qualities. Foam displaces blood and creates an increased effective contact area between the sclerosant and the endothelium and induces venous spasm.[14] Various methods and procedures have been described for creating a foamed sclerosant, but is in essence very straightforward. Foam is created by forcibly mixing liquid sclerosant with air, oxygen or carbon dioxide.[15,16,17]

Indications

Primary insufficient GSVs and SSVs as well as previously treated varicose veins and recurrences after surgery (for example due to neovascularization) can be treated with ultrasound-guided foam sclerotherapy. All sizes of GSVs, independent of CEAP class and type (linear and tortuous), can be treated safely and effectively (see Table I).[21] Small and large diameters, are successfully treated, but saphenous veins with diameters of 10 mm or more may require multiple treatments and relatively large volumes of foam (up to 3 sessions and 15 cc of foam).[23] UGFS can be used in patients with severe chronic venous insufficiency (CVI) and may enhance ulcer healing.[19] Also perforator veins and congenital venous malformations have been treated with this technique.[24-26]

Suitability of a patient for foam sclerotherapy depends on the aims of treatment as well as the venous anatomy. The main advantage of foam sclerotherapy is that it can be carried out successfully in almost any patient with clinically significant venous disease, although morbid obesity, old age or frailty and severe concomitant diseases may entangle the intervention. Moreover, the procedure is swift and takes a couple of minutes. The only absolute contraindications are severe allergy to aethoxysclerol and, as for all venous therapies, obliteration of the deep veins. Patients should be fully informed about the method of treatment as well as the complications that may arise. They should be warned about the (inflamed)

lumps caused by thrombophlebitis and the chance of skin hyperpigmentation. Deep venous trombosis (DVT) is also an alleged serious complication that should be mentioned as well as severe allergy, although both are very uncommon.

Table I: Indications for the different minimal invasive treatments of varicose veins.

Indications	UGFS	EVLA	RFA
GSV	+	+	+
SSV	+	+	+
Accessory veins	+	+/-	+/-
Perforator veins	+	+/-	+/-[a]
Diameter <0.5 cm	+	-	+/-
Diameter 0.5-1.0 cm	+	+	+
Diameter >1.0 cm	+/-	+	+[b]
Tortuous vein	+	-	-
Neovascularization[c]	+	-	-
Partial intraluminal obstruction(s)[d]	+	-	-

[a] mini-RFA can be used
[b] maximum vein diameter equals 12 mm in conventional RFA, not in fast version
[c] may occur after surgical stripping
[d] after thromboflebitis, UGFS, EVLA, or RFA treatment

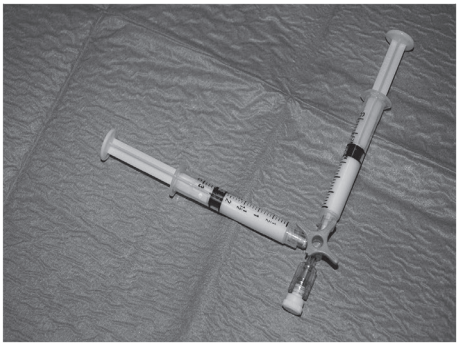
Procedure

The most common method of producing foam is the Tessari-method. In this method, two syringes are connected by a three-way valve, and the liquid sclerosant (1 cc aethoxysclerol or sodium tetradecyl sulfate 1-3% in Europe and the USA), is forcibly mixed with air (3-4cc) and frothed into foam by a pumping action (Figure 1a). The liquid sclerosing solution, which is used in classic sclerotherapy, is mixed with air to create foam. This foam of fine bubbles is injected intravenously with ultrasound (US) guidance. In classic sclerotherapy, the air block technique (i.e., first inject an air bubble before injecting the sclerosant) has been used to prolong contact time with the venous wall and to reduce the 'wash out' of the agent that is injected in the vein.[16]

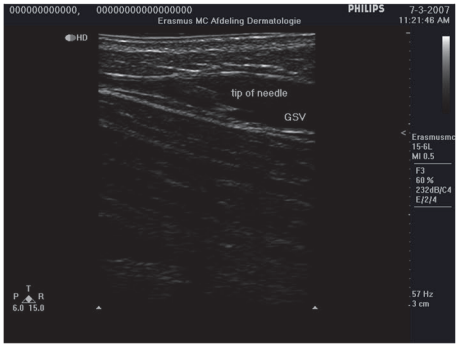
Foam is usually administered at one or more points of the saphenous varicose vein while the patient is in horizontal position. Ideally, the first bolus of foam (3-5cc) is administered in the proximal part of the treated vein and subsequent injections more distally because most of the foam moves in the direction of venous flow. In the 2nd European Consensus it is recommended to inject at the proximal thigh ten centimeters below the saphenofemoral junction in order to achieve optimal occlusion of the proximal part of the vein.[27] The vein is visualized longitudinally by ultrasound to guide and control venous access (Figure 1b). The foam can be injected directly or through a cannula, catheter or butterfly needle.[17,28] The echodens foam is clearly visible,

confirming proper injection (Figure 1c and d). The volume of injected foam depends on the length and diameter of the vessel and may range between 3-50 ml per session. There is no high level of evidence on how much the maximum volume of foam should be per treatment session; this is highly variable between physicians. The suggestion not to exceed 10 ml per session in the 2nd European Consensus is based on expert opinion. For saphenous varicose veins, a foam that is made of 3% aethoxysclerol appears to be modestly more effective than a foam made of 1% aethoxysclerol but it is more frequently associated with adverse events such as hyperpigmentation and phlebitis.[29] After injection, the patient remains horizontally or in reverse Trendelenburg position for at least 5 minutes, to enhance contact time of the foam with the venous wall. After therapy, cotton wool or foam pads can be applied over the tract of the veins and compression therapy (bandages, anti-thromboembolism stockings and/or medical elastic compression stockings class II) are recommended for a period that varies between physicians from one to six weeks.

Figure 1: Creation of foam (**A**); gaining access to varicose vein (**B**); injection of foam in cross-sectional view before (**C**) and after injection (**D**).



A



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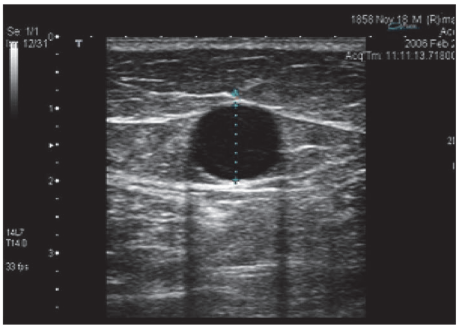

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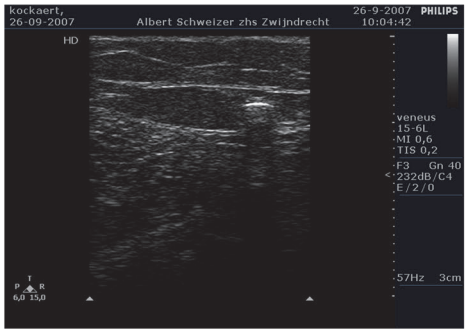


D

Efficacy

Foam sclerotherapy is about four times more effective than the classic liquid sclerotherapy, because of the increased contact time with the venous wall, increased surface area, and the induction of venous spasm.[22] In several studies, about two thirds of the saphenous varicose veins were occluded after one UGFS session and more than 90% of treatments were successful after two or three sessions.[19,20,29] Several large case series [18,29] and one multicentre study[30] have been published but very few comparative studies have been performed.

Ceulen and colleagues showed occlusion in 88% of GSVs and 82% of SSVs after treatment with UGFS in 1411 limbs after a mean follow-up of 11 months.[29] Smaller series showed 69% complete sclerosis in 99 limbs after 24 months of follow-up,[23] 44% occlusion in 211 limbs after 5 years of follow-up[31] and 88% occlusion in 143 limbs after 6 weeks of follow-up.[19] Cabrera et al.[26] published a case series of 500 legs treated with foam sclerotherapy. He reported that after three or more years 81% of treated GSVs remained occluded and 97% of superficial varicose veins had disappeared. This required one session of sclerotherapy in 86% of patients, two in 11% and three sessions in 3% of patients. Subsequently, a number of authors have published clinical series based on this technique including Frullini and Cavezzi,[18] who reported a series of 453 patients, and Barrett et al.,[23] who reported a series of 100 limbs. Cavezzi et al.[32] has subsequently published a detailed analysis of the efficacy of foam sclerotherapy in 194 patients, reporting a good outcome in 93% of patients. UGFS was an effective treatment for the SSV, with abolition of reflux and visible varicose veins, and improvement in HRQoL for at least 12 months.[33] Obliteration rate of the GSV one day post-procedure was high with 94% of treated limbs. Ultrasound examination showed complete thrombosis of these veins with complete elimination of retrograde flow in the GSV. This efficacy is similar to, or even better than the reported obliteration rates of 60%-99% in the English literature.[17] Foam sclerotherapy has shown to be an effective treatment for primary varicose veins in the lower limbs by obliteration of the GSV. Unlike surgery, this treatment does not require general, spinal, or local anaesthesia. Furthermore, the treatment time is shorter and the recovery faster. In comparison with other endovascular techniques such as EVLA and RFA, the use of foam as obliteration method is significantly more cost-effective.

Safety

The most common adverse events (Table II) associated with foam sclerotherapy are thrombophlebitis, matting, hyperpigmentation, and pain provoked by injection or pain persisting at the sclerosed area.[34] The minor complications in the immediate post-procedure period include hyperpigmentation (6.1%), superficial thrombophlebitis (7.6%) and cellulitis (1.5%). These local effects are mostly mild and may represent the spectrum of the inflammatory effect of the sclerosant. In several trials and case series, the rate of deep venous thrombosis varied from 0%-6%.[34]

Table II: Likelihood of specific adverse events associated with each of the three minimal invasive techniques.

	UGFS	EVLA	RFA
Allergic reaction	+	-*	-*
Skin necrosis / burns	+/-	+	+/-
Ecchymosis	+/-	+	-
Pain ('pulling chord') due to venous contraction	-	+	+/-
Thrombophlebitis	+	+	+
Deep venous thrombosis and emboli	+	+/-	+/-
Nerve damage (peripheral)	+/-	+/-	+
Pigmentation	+	+/-	+/-
Matting	+	-	-
Scotoma (transient)	+	-	-
Central neurological symptoms (transient)	+	-	-

UGFS ultrasound guided foam sclerotherapy
EVLA endovenous laser ablation
RFA radiofrequency ablation
* Allergic reaction to local anesthesia can occur

Local cutaneous side effects such as hyperpigmentation and, very rarely, skin necrosis can result from after extravenous injection of foam. Foam sclerotherapy is, in comparison to classic liquid sclerotherapy, more likely to induce post inflammatory hyperpigmentation but less likely to induce skin necrosis because it has a much higher sclerosing power at a 3-4 time dilution. A few weeks after therapy, patients may complain of a strand-like induration of the injected vein due to venous obliteration. Most of the adverse events are comparable with those after liquid sclerotherapy and include rare events such as migraine-like neurological symptoms and scotomas, especially in people with an open foramen ovale. Although the moving sclerosing foam enters the systemic circulation and is detected in the right ventricle of the heart seconds after administration,[29] very few DVT[34] and emboli have been reported.[35] The likelihood of these serious side effects may depend on the volume of injected foam.[16] Some authors recommend the use of low molecular weight heparins (LMWH) for 5 days to prevent DVT, especially in patients with a higher risk for thromboembolic complications.[27,28]

Summary

Ultrasound-guided foam sclerotherapy is a safe and effective treatment for superficial saphenous insufficiency. This treatment is swift, inexpensive and is indicated for the treatment of both primary and recurrent varicose veins. However, UGFS of large subcutaneous branches may induce thrombophlebitis.

ENDOVENOUS LASER ABLATION (EVLA)

In 2001, Navarro and Min published the first case series of a novel way to use laser energy through an endoluminal laser fiber for the treatment of saphenous varicose veins, with the objective to eliminate the highest point of reflux and to obliterate the incompetent segment and with the secondary aim to increase patient's comfort, and to reduce procedure-related costs and risks.[36,37]

Despite consensus on the requirement of a thermally damaged venous wall, the uncertainty relates to the mechanism or mechanisms that are responsible for the thermal injury. Laser energy is delivered endovenously from the fiber tip and is highly focused, and the temperature close to the fiber tip can rise to 1000°C.[38,39] The high temperature that is caused by the laser energy may induce multiple (micro)perforations of the venous wall.[40,41] Three other mechanisms, besides the direct contact that results in micro perforations, have been proposed: (1) direct laser light absorption by the vein wall,[38,42] (2) steam bubble generation at the fiber tip[43,44] and (3) heat conduction from the fiber tip.[45]

Indications

EVLA can be used for the treatment of a selected type of insufficient GSVs and SSVs (Table I). Linear primary saphenous varicose veins with a diameter of at least 4-5 mm are ideal for EVLA, because of the rigidity and size of the disposables. For more tortuous veins such as the accessory veins and perforator veins, thinner fibers can be used.[46,47] Caution is indicated, in the treatment of large parts of recurrent varicose veins, because introducing the laser fiber may be difficult and there might be more risk of inducing embolic events or perforation of the vein. However, EVLA can be used for smaller proximal segments (5-10 cm in length) of recurrent saphenous veins, which is in accordance with a surgical re-ligation, in combination with phlebectomy and/or UGFS of the distal parts of the recurrent varicose vein.

Procedure

One of the benefits of EVLA, in comparison to stripping, is that it can be performed under local tumescent anesthesia in an outpatient setting. Venous access is obtained by puncturing the vein with a 16 or 18 French needle under US guidance and only in a minority of cases by direct exposure through a phlebectomy incision (Figure 2a). Most commonly, the insufficient GSV is entered at knee level because of ease of access (i.e., large diameter and linear course) and the smaller risk of nerve injury. If possible, identified causes of venous insufficiency, such as insufficient perforator veins (e.g., Boyd's, Dodd's or May's perforator) should be treated concurrently. After entrance to the varicose vein is established, a guide wire is passed through the hollow needle into the vein until beyond the junction. If the varicose vein is too tortuous, has a small diameter (due to spasm), large side branches, or contains thrombotic or sclerotic fragments (after a phlebitis or prior treatment, respectively), advancing the wire can be difficult

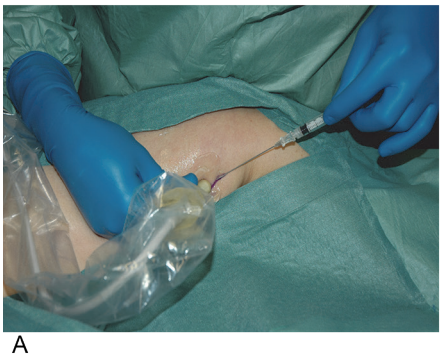
and caution is indicated because of the enhanced risk of perforation and embolic events. After the guide wire is in place, the needle is removed and a small cutaneous incision of 3 mm is made, an introducer sheath will pass over the guide wire and will be positioned a few centimeters below the junction (Figure 2b). Subsequently, the laser fiber (diameter ranges between 200 to 600 micrometer) can be introduced after removing the guide wire (Figure 2c). There are disposable EVLA sets that no longer use the guide wire and/or have the EVLA fiber already inserted in the sheath. The most pivotal step in the EVLA procedure is positioning the echo dense tip of the sheath 1 to 2 cm distally from the junction under longitudinal US visualization (Figure 2b). The wavelengths that are used in EVLA target (deoxygenated) hemoglobin and/or water and range between 810 and 1500 nm). About 250-500 ml (depending on the length of treated vein) of tumescent anesthesia (5 ml epinephrine, [5 ml bicarbonate] and 35 ml lidocaine 1% diluted in 500 ml saline or ringers lactate) is administered into the perivenous space under US guidance (Figure 2d) using a syringe or mechanical infusion pump. Tumescent anesthesia is warranted because it reduces pain, cools perivenous tissue and decreases the venous diameter. After activation, the laser is pulled back continuously (about 2-5 mm/s, depending on the power and wavelength that is used) (with 1320 nm laser, a pull-back speed of 1 mm/s is commonly used)[48] or in a pulsed fashion with the objective to administer about 50-70 Joule/cm.

Efficacy

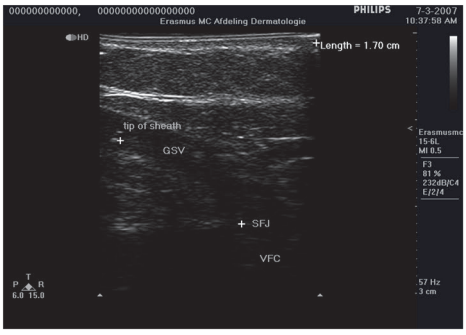
Multiple case-series (number of treated limbs ranging from 6 to 1250) have been presented and systematic reviews have been published.[49,50,51] Although EVLA's success rate decreases slightly in time, it remains at least 90% in the majority of the studies.[50] In a prospective study, 93% of 499 GSVs were occluded 2 years after therapy; an Italian workgroup reported a success rate of 97% in 1000 patients with a follow-up of 3 years and another large study with more than 1250 limbs treated showed a success rate of approximately 95%.[52-54] In a combined 4 year follow up study looking at endovascular laser ablation combined with ambulatory phlebectomies for the treatment of superficial venous incompetence using an 815 nm diode laser, a recurrence rate of 4.3% at 4-years, 3.6% at 2 years and 5.9% at 1 year was found with the majority of recurrences after 1 year of follow-up.[55]

Myers and Jolley recently reported a successrate of 76% in 509 GVSs at 4 years of follow-up using life-table analysis. After secondary treatment by ultrasound guided sclerotherapy of the recurred varicose veins, the successrate increased to 97%.[56] In the recent study by Ravi and colleagues, in which 2841 saphenous varicose veins were treated with EVLA, US examination after therapy showed a success rate of 98% for the GSV and 93% for the SSV. Of this large group of patients, 105 patients were participating in an annual follow-up study with a mean follow-up of 6.7 years.[57]

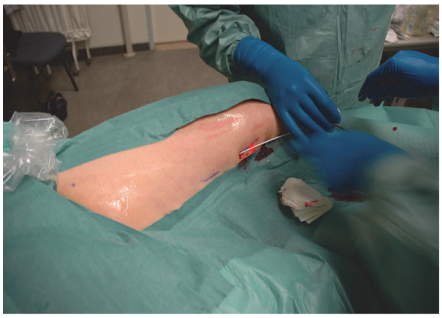
Figure 2: Gaining access to varicose vein under ultrasound examination (**A**); positioning of tip about 2 cm from the junction (**B**); passing through of the laser fibre through the sheath (**C**); application of tumescent anesthesia (**D**).



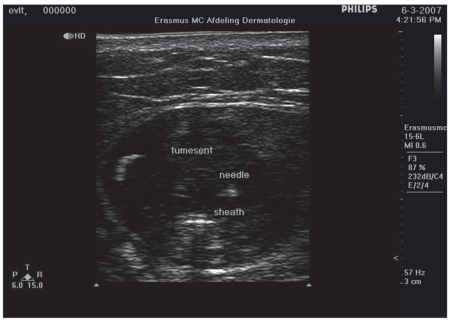
A



B



C



D

Safety

The multiple microperforations of the venous wall, which are induced by the high temperature creating by the laser energy and direct contact of the fiber tip with the venous wall, often result in mild-to-moderate pain ('pulling cord') and moderate bruising. These common adverse events disappear spontaneously within one or two weeks and can be managed by medical elastic compression stockings and painkillers.[56] Although minimally invasive techniques may reduce side-effects associated with surgery (e.g., wound infection and scarring), they may be associated with DVT and skin burns (especially when tumescent anesthesia is not properly used), but both are very rare. EVLA induces a symmetrical and non-floating sclerosis. From this treatment-induced sclerosis a thrombus may progress into the deep venous system creating a DVT (thrombus extension), usually asymptomatic. However, the likelihood of DVT is less than 1%.[52-54,58] In addition to careful instructing the patient, some authors advise performing US

examination one week after EVLA to exclude DVT and others prescribe LMWH for 5-7 days after the procedure to prevent the development of DVT.[59] Skin burns are also rare and may occur when the distributed amount of energy is too high, when superficial veins are treated, or when the cooling effect of the tumescent anesthesia is insufficient. Extra caution is needed when treating the extrafascial part of the saphenous varicose vein and at the cutaneous exit site of the laser fiber. Superficial thrombosis, dysesthesia, hematoma, cellulitis and arteriovenous fistula have been reported after EVLA (Table II).[52,56,59,60]

Summary

Endovenous laser ablation has shown to be one of the most effective treatments for primary insufficient GSV and SSV: the overall rate of satisfaction, symptoms relief and absence of varicose veins was 86%[54] and a success rate of at least 90%.[50] Also, EVLA procedures are considered to be safe, well-tolerated, and are associated with minimal complications.[57,58]

ENDOVENOUS RADIOFREQUENCY ABLATION (RFA)

Since 2000, several case series have been published about the use of RFA in the treatment of lower extremity varicose veins.[61-65]

The temperature-controlled endovenous radiofrequency ablation is accomplished by endoluminal application of radiofrequency energy directed into the vein wall with specially designed configurations of bipolar electrodes. Additionally, control of radiofrequency energy delivery using a temperature feedback loop allows the intima of the vein to be maintained at or near a predetermined setpoint temperature during catheter pullback through the vein. The length of time a section of vein wall is exposed to the setpoint temperature is determined by the speed at which the catheter is withdrawn along the vein segment to be treated.[66] RFA works by heating the vein wall in its whole circumference. Endovenous temperatures are controlled between 85° to 90°C,[38] and causes collagen shrinking in state of destruction and carbonisation which is seen in treatment with EVLA.

Recently, a new segmental catheter (VNUSClosure Fast® VNUS Medical Technologies, Inc, Sunnyvale CA) has been introduced, which has a segment of 7 cm that heats to 120 degrees Celsius.[69] This technique is much faster than the previous radiofrequency catheters. The special operating parameters to provide sufficient energy to heat the vein wall and cause collagen contraction and destruction of the vein wall, while limiting the degree of perivascular heating. Microscopic examination of the vein wall after treatment does not show carbonisation, in contrast to veins treated with EVLA. Procedural advances, such as ultrasound-guided tumescent infiltration along the course of the vein to be treated, have provided an added level of thermal protection to the perivenous tissue during the application of radiofrequency energy.[66]

Indications

The indications for RFA are comparable to EVLA, except that RFA cannot be used to treat veins with diameters greater than 12 mm (Table I). A 5-F catheter (1.7 mm) is used for veins with a diameter of 2-8 mm and an 8-F (2.7 mm) catheter can be used for veins as large as 12 mm. The new segmental fiber is one size and can be used independent of vein diameter. Because of the rigidity and size of the catheter, caution is indicated in tortuous and relatively small varicose veins to avoid perforation.

Procedure

In accordance with EVLA, RFA can be performed in an ambulatory setting. Access to the varicose vein is obtained with a 16 Gauge needle under US guidance usually at or below knee level or distally from the point of reflux. The RFA catheter is positioned in the close proximity of the saphenous junction. The pods of the catheter are expanded in the common femoral vein and, with US guidance, withdrawn into the orifice of the junction. A cuff or bandage can be used to compress the blood out of the vein. The small electrodes at the end of the 'umbrella' catheter are in direct contact with the venous wall and omit high radiofrequency energy (regulated by power, impedance and time) that is generated by a radiofrequency generator. The radiofrequency waves heat the local tissue at the site of direct contact to 85 or 90 degrees Celsius, causing collagen shrinkage, denudation of endothelial and obliteration of the venous lumen.[66] A thermocouple monitors the temperature during treatment. Similar to EVLA, perivenous tumescent anesthesia is applied (Figure 2d) to increase contact surface and to decrease the pain sensation and the risk of dysesthesia.[67] Also, manual compression is recommended during the treatment in order to enhance contact of the catheter with the venous wall. The catheter is slowly pulled back with a speed of approximately 3 cm/min (total pull back time is about 20 minutes on average for the GSV between SFJ and knee level) but can be faster at higher temperatures.[68] Compressive bandages or medical elastic compression stockings are indicated for one or two weeks after treatment.

The segmental RFA catheter is much faster than the previous radiofrequency catheters and the first case series of 252 treated GSVs showed an occlusion rate of 99.6%.[70]

Efficacy

Since 2000, several case series have been published showing that RFA can be successfully used in the treatment of lower extremity varicose veins.[61-65] The first long-term, large, single centre case series showed that RFA was effective in about 90% of 140 limbs after two years of follow-up.[67] This study also showed that 98% of patients were satisfied with the treatment and would recommend it to a friend. A multicenter study that included 1006 persons (1222 limbs) showed good anatomical success rates of 88,8% occlusion and patient satisfaction in more than 85% of the people after 4 years of follow-up.[71]

Safety

Because important procedural changes have been made after the earliest case series of RFA serious side effects such paresthesia, skin burns and DVT, are barely reported. One study found 16% DVT in 73 limbs treated with RFA, and presented this number with 'a word of caution'.[72] However, this study may be considered as an exception, because most studies report DVT in less than 1% of treated limbs.[57,73,74] Initially, paresthesia was reported relatively frequent, but the incidence decreased significantly after the use of tumescent anesthesia.[67, 75] Possibly because the temperature in RFA is lower and the energy in RFA is distributed in a different way than the laser energy,[38,39] the local RFA induced adverse events, such as pain and ecchymosis, are milder compared to EVLA. Skin burns and phlebitis are reported in about 2-5% of cases (Table II).[75]

Summary

There is sufficient evidence to conclude that endovenous RFA is a safe and effective treatment for saphenous insufficiency. The RFA catheters are more expensive than most EVLA disposables. This treatment is best suitable for the management of primary uncomplicated varicose veins with a diameter of at least 5 mm but less then 12mm. More studies assessing the segmental RFA catheters are warranted.

COMPARISON OF THERAPIES

The minimally invasive therapies that are described above have shown to be very effective and safe. Unfortunately, there is a lack of well-performed randomised comparative studies. Some studies are currently ongoing. Recently a meta-analysis was published that showed a pooled success rate for stripping, foam sclerotherapy, radiofrequency ablation, and laser therapy of about 78%, 77%, 84%, and 94%, respectively. After adjustment for follow-up, EVLA was significantly more effective compared with the other three therapies.[76]

UGFS versus Surgery

Hobbs and Rutgers have both demonstrated that liquid classic sclerotherapy is not as effective as surgical stripping.[77,78] Though a small prospective randomized trial suggested that SFJ ligation and one session of UGFS was less effective in the short term, but significantly less costly and time consuming than SFJ ligation, stripping and multiple avulsions.[79] Recently, Darvall[80] published in a nonrandomized observational study that patients who had surgery were more likely to have significant bruising (44 *versus* 7.2 per cent; p<.001) and pain (17 *versus* 5.5 per cent; p=.001) compared with UGFS. UGFS was associated with less time off work (43.2% of patients returned to work within 24 h, whereas none of the patients who had surgery did so (p<.001)) and the UGFS group was able to return to driving earlier (within 4 days, p=.014). In comparative studies, the risk of adverse events compared between foam sclerotherapy and

other treatments was not significantly different. However, in the French registry[35] the risk of visual disturbance was significantly higher for foam compared with liquid sclerotherapy.

EVLA versus Stripping

Three small short-term studies that compared EVLA with surgical stripping suggested that the clinical efficacy parameters were comparable, but EVLA had a significantly better effect on HRQoL.[81,82,83] A recent meta-analysis showed that EVLA was significantly more effective compared to stripping, UGFS and RFA.[76] Darwood concluded that abolition of reflux and improvement of disease-specific quality of life was comparable between EVLA and surgery. Patients return earlier to their normal activities after EVLA, this may have an important socio-economic advantage.[84] After 2 years the recurrence of varicose veins was similar after surgery and EVLA, although the neovascularisation, a predictor of future recurrence, was less common after EVLA.[85] Although cost-effectiveness studies are lacking, EVLA is likely to reduce costs because there is less down-time after EVLA and it can be performed in an outpatient setting.[86]

RFA versus EVLA

RFA and EVLA differ in the delivery of thermal energy to the vein wall as is described before. Because of the high temperature and the direct contact of the focused laser beam with the vein wall, EVLA, is generally associated with vein wall perforations whereas RFA seems to re-model and/or shrink the veins wall.[40,41] This is one of the reasons why EVLA seems to be associated with more treatment-related pain and indurations one or two weeks after therapy than RFA. The RECOVERY study observed that segmental RFA was significantly superior to EVLA in terms of HRQoL. The group that was treated with RFA had less complains of pain, ecchymosis and tenderness and had better HRQoL parameters than the group that was treated with EVLA.[87] Older retrospective studies showed an equal effect between RFA and EVLA,[88] and a significant higher closure rate for EVLA compared to RFA at 500 days (92% vs. 85%).[75]

RFA versus Stripping

Three small randomized clinical trials that compared RFA with stripping, demonstrated that the two therapies were about equally effective on the relatively short term, however patients treated with RFA reported less postoperative pain and physical limitations, faster recovery, fewer adverse events and superior HRQoL parameters compared to patients treated with surgical stripping.[89,90,91]

A recent meta-analysis on stripping and endovenous therapies showed that EVLA was significantly more effective than stripping ($p<.0001$), UGFS ($p<.0001$) and RFA ($p=.01$). No significant difference in effectiveness was observed between RFA versus stripping ($p=.14$) and RFA versus UGFS ($p=.13$).[76]

In clinical trial registries can be found that several RCTs such as RFA versus stripping and UGFS versus surgery are currently ongoing. Our study group is involved in a multicenter randomised controlled trial (MAGNA-trial) that compares stripping, EVLA, and UGFS.

DISCUSSION

Procedure

Each of the minimally invasive therapies can be performed in an outpatient setting. EVLA and RFA can be done using local tumescent anesthesia and UGFS does not require anesthesia. In contrast to UGFS, EVLA and RFA should be performed in a sterile environment. RFA is a patented and standardized procedure. Although the characteristics of the laser treatment, such as wavelength, mode of pulling back the fiber, power and pullback speed may vary, the procedure is relatively well standardized and it is widely accepted that 60 Joule/cm or more should be administered (but this may be less as well). Compared to RFA and EVLA, UGFS seems to vary more between physicians (for example, type and concentration of sclerosant used, the creation of foam, volume of foam needed, localization of injection, and one vs. multiple injections, type of compression therapy). Each of the minimal invasive techniques requires US experience, preferably performed by the physician but technicians may assist during the procedure. UGFS takes about 15 minutes whereas the endovenous therapies may take about 45 minutes. Of the three therapies, UGFS may be the most cost effective because it is fast, cheap, and easily repeated, but unfortunately, good studies are lacking. Although the period of using medical elastic compression stockings after UGFS is controversial (between 0-6 weeks), it seems to be essential in achieving an optimal result.

Efficacy

EVLA and RFA are equally effective compared to vein stripping but are more appreciated by patients.[87,88] However, one meta-analysis showed highest occlusion rates for EVLA.[76] The frequency of recurrence of varicose veins was similar in a comparitive study after two years of follow-up after surgery and EVLA, though there was slightly less neovascularization, which may be a predictor of recurrences, in the EVLA group.[85] UGFS is very effective for treating saphenous recurrences after vein stripping, because these recurrent veins are usually tortuous, are not located outside the fascial blades and often have a relatively small diameter. In veins with very large diameter EVLA may be the best option, in comparison with the other minimal invasive treatments, because in these cases, UGFS often requires 3 or more treatment sessions and the RFA catheters are designed for a maximum diameter of 12 mm, except for the new segmental RFA catheter. UGFS is indicated, in small and symptomatic insufficient saphenous veins (diameter <4 mm) and recurrence of tortuous veins.

Safety

With each of the three minimal invasive treatments, the development of DVT is the main concern. This is because of the destruction and/or irritation of endothelial cells and the formation of a sclerosis (which is different from a thrombus, because it is symmetrical and adheres to the venous wall and has no free floating component). There are no comparative safety studies, but a comparison of the largest case series of each of the treatments suggests that the risk may be highest for RFA (up to 1%), which is comparable to the risk of DVT after vein stripping.[73,74,92] However, symptomatic and asymptomatic thromboembolic events and methods of diagnosis should be differentiated when comparing thromboembolic outcomes of these treatments. There are several opportunities mentioned to avoid the prevalence of DVT, such as hypercoagulability screen (for high-risk individuals selected by history and physical examination), low molecular weight heparin preoperative and/or postoperative (for about a week), US control of the junction following treatment after 1 week, localization of the catheter distal from the inferior epigastric vein, ample administration of tumescent anesthesia, avoidance of perforation, and for UGFS limb elevation, mobilization and applying pressure on the junction after injecting the foam, have been suggested to reduce the risk of DVT. However, these measures are controversial and there is no consensus on DVT prevention.

Among the most common serious side affects of saphenous stripping is neurological damage. In about 7% in short and 40% in long stripping of the GSV, nerve damage occurs.[93,94] Although the incidence is significantly lower compared to surgery, paresthesia has been reported for UGFS, EVLA and RFA due to extravenous injection of foam or increased perivenous temperature, respectively. In accordance with surgery, the likelihood of nerve injury may increase when EVLA and RFA procedures are started at the ankle and extra tumescent in the popliteal fossa should be administered in the EVLA and RFA treatment of the SSV to avoid sural nerve damage.

With endovenous techniques no or minimal scars are created and the risk of wound infection is very low in contrast to surgery. However, each of the minimally invasive techniques may be associated with local cutaneous side effects. Skin burns have been reported in less than 1% after EVLA and RFA procedures and can be easily avoided by applying a sufficient volume of tumescent anesthesia. Hyperpigmentation and to a lesser extent skin necrosis has been reported after UGFS. Postoperative pain and ecchymoses along the treated vein are very common after EVLA (for about 2 weeks and are controlled by NSAIDs) and to a lesser extent after RFA and UGFS.

Recurrence of varicose veins after stripping is thought to be due to neovascularization at the SFJ and occurs in about 25% of the patients 5 years after therapy.[95] This has been studied using US but has not been documented for UGFS, EVLA and RFA. This may be because these techniques, in contrast to surgery, do not disrupt the endothelial lining and do not eliminate other veins connected with the SFJ. This difference may explain the high long-term success

rates of the three minimally invasive procedures. Endovenous therapies show anatomical failure in about 10%, with (partial) recanalization of the treated vein but these failures are not always clinically important failures.

Steam ablation is a new and promising endovenous thermal therapy, but there are no data on steam ablation of varicose veins available yet. A randomized controlled trial is going on in our centrum, which compares EVLA with steam ablation.

Conclusion

Additional comparative studies between minimally invasive treatments and surgery are needed to assess the difference in efficacy, patient reported outcomes including HRQoL and to determine the most cost-effective therapy. EVLA seems to be the endovenous treatment that is most commonly used, because it is less expensive and faster than standard RFA. However, UGFS may be the most cost-effective therapy, but several treatment sessions may be needed.

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Chapter 3

Validation of the Chronic Venous Insufficiency Quality of Life Questionnaire in Dutch Patients Treated for Varicose Veins

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ABSTRACT

Background: The Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) is a disease specific instrument, to measure the impact of chronic venous insufficiency (CVI) on patients' lives. The objective of this study is to test the psychometric properties of the CIVIQ, and to validate the use of the questionnaire translated in Dutch.

Methods: A standardized questionnaire, including CIVIQ and SF-36 was obtained before and 1 month after treatment to al new patients with varicose veins. The feasibility was tested by missing responses and response distribution. CIVIQ's scores were compared to the SF-36 scores and between different levels of severity of varicose veins. The CIVIQ's reliability was assessed using Cronbach's alpha and test-retest reliability. The structure was studied using factor analysis. The scores before and after therapy were compared to assess responsiveness.

Results: There was a response rate of 93.5%. None of 20 items missed less than 10% of responses, but 3 showed ceiling effect. The CIVIQ correlated well with the physical and moderately with the mental MCS of the SF-36 suggesting a good construct validity of the CIVIQ. The median CIVIQ scores increased significantly with the severity of varicose veins. The CIVIQ showed an excellent internal consistency and an excellent test-retest reliability. The CIVIQ score decreased in 75.65% after treatment. The results were in accordance with the Norman's rule and showed a median effect size.

Conclusion: This study confirms the feasibility, validity, reliability and responsiveness of the CIVIQ in patients with varicose veins. The psychometric properties of the Dutch CIVIQ were comparable to the original French version.

INTRODUCTION

Signs of chronic venous insufficiency (CVI) may be found in about half the adult general population and about a quarter of the people has lower-extremity varicose veins.[1] In addition to cosmetic impairment which may lead to psychological discomfort, common symptoms of CVI and varices are aching, tired feeling in legs, discomfort, edema, restless legs and muscle cramps. The complications of CVI and varicose veins include eczema, lipodermatosclerosis, "atrophy blanche", superficial thrombophlebitis and venous ulcers. Not surprisingly, patients suffering from CVI may have substantial health related quality of life (HRQoL) impairment because of the appearance of varicose veins, the symptoms and complications of CVI.[2] Several studies confirmed that treatment of venous disease improved HRQoL.[3-7] In addition to generic HRQoL instruments such as the SF-36 and EQ-5D, which have been used in patients with CVI,[3-5] disease specific instruments provide more specific information about the impact of CVI and varicose veins on patients' everyday lives. The two most commonly used disease specific HRQoL tools for varicose veins and CVI are the Aberdeen Varicose Vein Questionnaire (AVVQ)[9,10] and the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ).[2] The focus of the AVVQ is on the presence of symptoms (i.e., pain and itch) and clinical signs (i.e., swelling, discoloration, eczema and ulcer). Only 4 of 13 items address the psychological impact of varicose veins, especially the functioning domain.[11,12] Therefore, the AVVQ reflects the clinical disease severity and less the impact of the disease on a patient's life. In contrast to the AVVQ, the CIVIQ has been focussed more on the psychosocial impact of venous disease of the lower limbs (i.e., its effect on every day life).[2]

The CIVIQ was developed by Launois et al. in 1996.[2] This disease specific questionnaire demonstrated to be valid, to have an excellent internal consistency, a high reproducibility and a high responsiveness. It appears to be a valuable instrument for assessing improvement in patients' HRQoL in both clinical practice and trials.[13] Although the CIVIQ has been frequently used and is available in 13 languages, it's psychometric properties are not well documented in populations other than the original study.[6,13-19] The objective of this study is to test several psychometric properties of the CIVIQ in a heterogeneous group of Dutch patients treated for varicose veins.

METHODS

Study population

Between October 2008 and March 2009, all new patients who consulted the departments of dermatology and vascular surgery of the Catharina Hospital (Eindhoven, the Netherlands) for varicose veins were asked to participate in this study. At their first visits, patients were asked to complete the initial standardized questionnaire (defined as CIVIQ-1). In addition, half of the participants were requested to complete the HRQoL questionnaire again on the day prior to therapy and return them at the treatment day (i.e., CIVIQ-2). Subsequently, all patients were

asked to complete a third questionnaire at their follow up visit, which was at least four weeks after therapy (i.e., CIVIQ-3). Therapy consisted of surgical, non-surgical or a combination of these. The responsible physician was asked to record the 'C' of the CEAP classification and all performed therapies for each study patient.

Questionnaire

Together with a standardized questionnaire, which was self-administered and included questions about demographic and disease characteristics, the SF-36 and the CIVIQ (Appendix I) were included at all visits. The 20 questions of the CIVIQ (Table I) result in a global score and four separate domain scores: physical (items 5, 6, 7 and 9), psychological (items 12-20) and social impairment (items 8, 10 and 11) and level of pain (items 1, 2, 3 and 4). All questions have a 5-point response category with higher scores reflecting more severe impairment. Three separate scores can be calculated: a score per item (1 to 5), a score of each of the 4 dimensions (0 to 100) and a global score (value 0 to 100). Higher scores represent lower HRQoL due to CVI or varicose veins.[2]

The translation of the CIVIQ into Dutch was based on forward-backward translation as recommended.[20] In brief, three translators, all native speakers in Dutch, independently translated the questions and the response options of the English CIVIQ into Dutch. They were instructed to pay attention to conceptual rather than literal equivalence, and to choose words and language constructions that were as simple as possible. The translators were two employees of a registered translation office and a dermatologist. The three resulting independent forward translations were compared and discussed in a group meeting of the three translators. Differences were documented and discussed until consensus was reached about the optimal phrasing of the Dutch CIVIQ. This common forward translation was then given to two translators who were native speakers in English and fluent in Dutch. They each produced a backward translation that was both compared to the English CIVIQ for conceptual equivalence with the original source version. The analysis was documented and necessary adaptations to the Dutch CIVIQ version were made. The resulting Dutch CIVIQ was then administrated to twenty patients with venous disease of the lower limbs to provide qualitative testing of readability and comprehension. Because this qualitative testing revealed no problem with the Dutch CIVIQ, it was subsequently administered in the study population to collect data for psychometric analysis (Appendix 1).

The SF-36 is a generic HRQoL instrument and has proven applicability in several areas of disease including varicose veins.[3-5,7,22-24] The 36 items can be grouped in a mental and physical component scale (MCS and PCS, respectively). We included the SF-36 to test construct validity.

Table I: English version of the CIVIQ.

1.	In the past four weeks, if you have felt pain in the ankles or legs, what was the intensity of the pain?
2.	During the past four weeks, to what extent did you feel bothered / limited in your work or your other daily activities because of your leg problem?
3.	During the past four weeks, did you sleep bad because of your legs problems, and how often?
	During the past four weeks, to what extent dit your leg problems bother/limit you while doing the movements or activities listed below?
4.	standing for a long time
5.	climbing stairs
6.	crouching, kneeling
7.	walking briskly
8.	travel by car, bus, plane
9.	housework such as working in the kitchen, carrying a child, ironing, cleaning floors or furniture, doing handy work
10.	going to discos, weddings, parties, cocktails
11.	sporting activities, making physically strenuous efforts
	Leg problems can also have an effect on one's morale. To what extent do the following sentences correspond to the way you felt during the past four weeks?
12.	I feel on edge
13.	I become tired quickly
14.	I feel I am a burden to people
15.	I must always take precautions (such as to stretch my legs, to avoid standing for a long time…)
16.	I am embarrassed to show my legs
17.	I get irritated easily
18.	I feel handicapped
19.	I have difficulty going in the morning
20.	I do not feel like going out

ANALYSIS

Feasibility

The feasibility of the CIVIQ was evaluated by the overall response rate. Item difficulty was present if 10% or more of the answers of individual items were missing. The score distribution of all individual items was evaluated by assessing their floor and ceiling effects (i.e., 70% or more of the respondents exhibited the worst or best possible score). If an item loaded less than 0.40 on the main component of a confirmative principal component analysis it was considered complex.[8]

Patients with 3 or more missing scores were excluded from the analysis, except from the feasibility assessment. Missing values were replaced by the median of the completed items reported by an individual.

Structure

Before analysis, a confirmative principal axis factoring (PAF) followed by promax rotation was performed to test the structure of the CIVIQ with four dimensions.[19] This PAF analysis reflected 57.18% of the variance of the CIVIQ, but 9 of the 20 items did not load considerably (>0.40) on their original factor suggesting that the proposed structure of four dimensions was suboptimal. Therefore, in this study we have focussed on the global score of the CIVIQ and excluded its four subscales.

Reliability

Cronbach's alpha (reflecting the internal consistency of an instrument) was tested using the data from the first pre-therapy assessment and was considered good if between 0.7-0.9. The degree of test-retest reliability was estimated by Spearman correlation coefficients (Ω) of two assessments in the pre-treatment period about 4 weeks apart and was considered excellent if >0.80.

Validity

The construct validity of the CIVIQ (i.e., how it relates to other HRQoL measures) was tested calculating Spearman correlation coefficients (Ω) between patients' CIVIQ scores and the MCS and PCS of the SF-36. To test the convergent validity of the CIVIQ, we assumed that patients with higher level of clinical severity ('C' from the CEAP classification; C1 vs C2 vs C3-6) should have a significantly higher impact on HRQoL, which was tested using an ANOVA.

Responsiveness

Wilcoxon's signed ranks test was used to compare the CIVIQ scores prior to and after therapy, to estimate CIVIQ's sensitivity to changes brought about by treatment. To gauge whether the treatment related difference in CIVIQ scores was clinically relevant we used Norman's rule of thumb: if the change in score was more than half a standard deviation (SD) of the distribution of the CIVIQ score prior to therapy the change was considered clinically meaningful.[24] Effect size was used to measure the strength of the relationship between two variables in a statistical population. Effect sizes (d) were interpreted as follows: d=0.2-0.5 is considered a small effect size, d=0.5-0.8 is considered a medium effect size and d >0.8 is a large effect size.[25] Because C1 varicose veins can be considered a cosmetic condition, Norman's rule of thumb and the effect size were calculated for all patients and those with grades of C2 or more, separately.

The distribution of the global CIVIQ scores was nonparametric, therefore, it was represented by the median and its interquartile range (IQR). The other continuous variables will be presented by a mean and standard deviation (SD). Two sided p-values of 0.05 or less were considered statistically significant. All analysis were conducted using SPSS version 15.0. The Medical ethical committee of the Catharina Hospital (Eindhoven, The Netherlands) granted exempt status for this observational study. All participants provided written informed consent.

RESULTS

Study population

Of the eligible 170 patients with varicose veins who were invited to participate in this study, 159 patients (response rate 93.5%) completed the initial questionnaire (CIVIQ-1). After four weeks 80 participants were requested to complete a second questionnaire before treatment, to assess reproducibility, of which 73 (response rate 91%) returned the CIVIQ-2. The CIVIQ-3 (i.e., assessment at least 4 weeks after therapy) was completed by 93.5% of the 115 treated patients.

Of the 159 participants, 70.4% were women and the mean age of the study population was 53 years (SD 13.13, range 17-84; Table II). Classified according to C-component of CEAP classification, 14.5% of the participants were classified in 'C1', 37.1% in 'C2' and almost half in 'C3' levels or more. About half of the patients were considered 'treatment naïve' patients, those without previous treatment for varicose veins. The treatment of varicose veins during the study period was predominantly EVLA (and some had surgical ligation and stripping) in combination with phlebectomy and/or sclerotherapy (SCT).

Feasibility

Of the 159 patients who returned the CIVIQ-1, 10 patients (6.2 %) did not respond to 3 or more items. None of the individual items were considered suboptimal since missing responses varied between 0-9.4%. However, item 10 ('going out') and 11 ('sports/heavy work') were missing in 8.8% and 9.4% of the participants suggesting borderline feasibility of these items. Interestingly, 11 patients whose age ranged between 59-84 years did not respond to both these two items suggesting they were closely related.

Of the 20 items, three items demonstrated a substantial ceiling effect with 70% or more of the respondents indicating the lowest score (item 14 [74.8%]; item 18 [79.9%] and item 20 [84.9%]). This observation suggests that only few patients had the perception to 'constitute a burden to others', to 'feel disabled' or to 'be anxious to meet other people' because of the complaints of their legs. This suggests a poor discriminative effect of these three items for the presence of varicose veins. None of the items showed floor effects.

Table II. Demographic, disease and therapy characteristics of study population (159 patients).

Characteristics	No. of patients (%)
Sex	112 Women (70.4%) 35 Men (22%) 12 unknown
Age, mean (SD, range)	53 years (SD 13.13, range 17-84 year)
'C' of the CEAP classification	
C1	14,5%
C2	37.1%
C3	30.2%
C4	11.9%
C5	3.1%
C6	2.5 %
Unknown	0.6%
Previous therapies for varicose veins	78 (49.1%)
Sclerocompression therapy	49 (30.8%)
Phlebectomy	8 (5%)
Proximal GSV ligation (with or without stripping)	31 (19.5%)
Endovenous ablation	3 (1.9%)
Foam sclerotherapy	1 (0.6%)
Unknown	10 (6.3%)
Treated in study period	125
Not treated in study period	34
Therapy in study period (n=)	125
Sclerocompression therapy	43 (27.0%)
Phlebectomy	47 (29.6%)
Proximal GSV ligation (with or without stripping)	20 (12.6%)
Endovenous ablation	35 (22%)
Foam sclerotherapy	22 (13.8%)
Combination	57 (46.4%)
Phlebectomy and GSV ligation (n=14)	
Phlebectomy and EVLA (n=10)	
Other	3 (2.4%)
Currently affected leg	
Left	38 (23.9%)
Right	33 (20.8%)
Both	78 (49.1%)
Missing	10 (6.3%)
Questionnaire	
1. before treatment	159
2. before treatment, after 4 weeks	73
3. after treatment	115

Structure

PAF analysis showed that extracted of the first factor accounted for 43.7% of the variability of the CIVIQ. The loadings of the 20 CIVIQ items varied between 0.19-0.77. Item 16 showed item complexity with a loading of 0.19 on the factor and item 18 was borderline complex with a loading of 0.39.

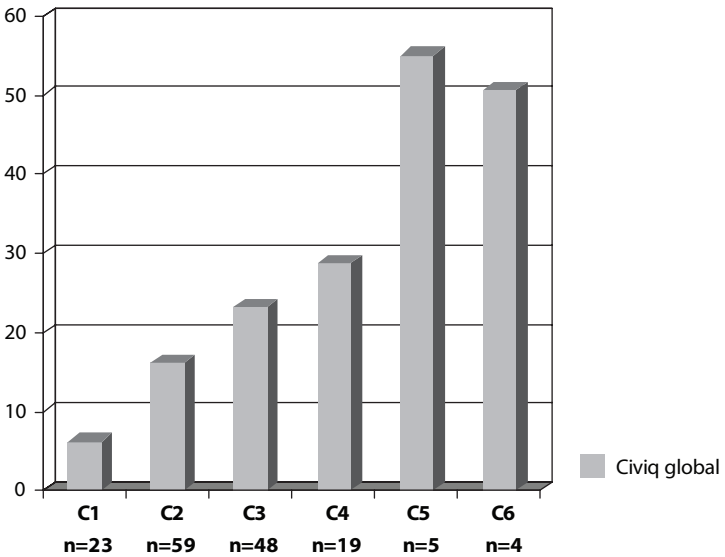
Reliability

The item responses of the CIVIQ-1 during the first assessment prior to therapy showed an excellent internal consistency (Cronbach's alpha=0.94). Among the 73 people who completed the CIVIQ twice prior to therapy (CIVIQ-1 and -2), the test-retest reliability of the CIVIQ was also excellent (Ω=0.86). The median global score of the CIVIQ-1 was 17.50 (IQR 8.13-33.75) and identical to the median score of CIVIQ-2 (17.50; IQR 7.50-33.75).

Validation

The CIVIQ-1 correlated well with the physical component scale (PCS) and moderately with the mental component scale (MCS) of the SF-36 (Ω=-0.64 and Ω=-0.42, respectively) suggesting a good construct validity of the CIVIQ in this population for the physical aspects but less for the mental aspects of having leg complaints. The median CIVIQ-1 scores increased significantly (Figure 1; p<0.001) with higher 'C' levels from 6.25 (IQR 2.50-13.75), 16.25 (IQR 12.50-32.50) to 23.13 (IQR 12.81-35.00) for 'C1', 'C2' and 'C3-6', respectively.

Figure 1: Correlation CIVIQ score and C-component of CEAP-classification.



Explanation: To test the convergent validity of the CIVIQ, we assumed that patients with higher level of clinical severity ('C' from the CEAP classification; C1 vs C2 vs C3-6) should have a significantly higher impact on HRQoL, which was tested using an ANOVA.

The median CIVIQ-1 scores increased significantly (p<0.001) with higher 'C' levels of from 6.25 (IQR 2.50-13.75), 16.25 (IQR 12.50-32.50) to 23.13 (IQR 12.81-35.00) for 'C1', 'C2' and 'C3-6', respectively.

Responsiveness

Of the 115 patients who were assessed prior to and at least four weeks after therapy (CIVIQ-1 and CIVIQ-3), the CIVIQ score decreased in 75.65% and increased in 16.52% of participants. The median CIVIQ score prior to therapy was 18.75 (IQR 11.25-33.75) and significantly decreased to 12.50 (IQR 5.00-22.50) after therapy. The mean global score decreased from 23.68 (SD 16.04) to 15.66 (SD 13.20). For all patients, the decrease in the mean CIVIQ score after therapy was 8.02 which was exactly half the SD of CIVIQ prior to therapy and is, therefore, in agreement with Norman's rule of thumb clinically significant. In accordance with Norman's rule of thumb, effect size of the CIVIQ was 0.50, which is considered a medium effect size suggesting that the treatment effect on patients HRQoL was clinically meaningful. Restricting the analyses to pre- and post treatment outcomes in 99 patients who were graded C2 or more showed that both Norman's rule of thumb was satisfied (8.42 vs 7.92) and the effect size increased to 0.53.

To specify between a treatment or a combination of treatments further analysis were made. The analysis showed that with EVLA alone (n=19) the median CIVIQ score prior to therapy was 25.00 (IQR 16.25-36.25) and decreased to 18.75 (IQR 12.50-28.75) after therapy. Significantly according norman's rule. Compared to treatment with EVLA in combination of phlebectomy (n=10) the median CIVIQ score prior to therapy was 20.63 (IQR 8.1-34.06) and decreased to 11.25 (IQR 1.25-15.93) after therapy. Significantly according norman's rule. Only few patients received EVLA in combination with Foam (n=3), sclerocompression (n=3), and/or crossectomy (n=3), although respectively the last two showed a significant decrease after therapy, no conclusions can be made because of the low sample size.

DISCUSSION

In this study, we have demonstrated that the CIVIQ is a feasible, valid, reliable and responsive tool in the assessment of HRQoL in patients with varicose disease. However, because the CIVIQ's four dimensional structure could not be confirmed, we recommend to use the global score of the CIVIQ only. It appears to be a reliable instrument but the extremely high internal consistency (>0.90) suggest some item redundancy, which was also observed in the initial validation study.[18]

The change in CIVIQ score after therapy for varicose veins was statistically significant and clinically meaningful, especially among patients with clinical relevant disease (C2 or more, according to CEAP classification). The tests analyzing the responsiveness of the CIVIQ confirm the importance of the concept of minimal clinical important difference (MCID), which implies that it is insufficient to only compare the HRQoL scores before and after therapy but also estimate the size of the effect and whether it is clinically relevant to the patient.[7] Categorization of CIVIQ scores using anchor-banding techniques would also be very useful for the interpretation of the scores because it would allow physicians to categorize patients' degree of HRQoL impairment.[8] Moreover, the responsiveness findings suggest that the CIVIQ

may not be the most optimal instrument to assess the impact of varicose veins that are a cosmetic problem only. In accordance with other studies, the CIVIQ correlated better with the PCS than the MCS of the SF-36 suggesting that the CIVIQ reflects the physical aspects better than the mental aspect of having varicose veins.[3-5] Similar findings have been reported for other varicose veins specific HRQoL tools such as the AVVQ and the VEINES-QOL.[12,27] This is further illustrated by the finding that the three items exhibiting poor discriminating properties (ceiling effects) were assessing the psychological impact of varicose veins suggesting that this domain may be less relevant to the majority of patients.

In addition to anatomical success rates, patient reported outcomes including some adverse events such as pain, HRQoL, treatment satisfaction and preference are increasingly recognised as meaningful outcomes in comparative clinical trials.[3,5,6] It is recommended to use a generic HRQoL instrument such as the SF-36 in conjunction with a disease specific instrument such as the CIVIQ or AVVQ because the latter two may provide more specific and detailed information about the impact of varicose veins and the effect of treatment.[8] Both the CIVIQ and AVVQ have now been validated in additional patient populations and are able to assess the impact of varicose veins on patients' lives. The main difference between these tools is that the AVVQ includes multiple items on symptoms, which may affect HRQoL but may be a different construct than HRQoL, and does not fully assess the psychosocial impact of varicose veins compared to the CIVIQ.

In conclusion, this study confirms the feasibility, validity, reliability and responsiveness of the CIVIQ in a Dutch population of outpatients with varicose veins. The psychometric properties of the Dutch CIVIQ were comparable to the original French version.[2,19]

APPENDIX 1

NEDERLANDSTALIGE CIVIQ

Veel mensen hebben klachten van onaangename gevoelens in hun benen, al dan niet in samenhang met zichtbare spataderen aan de benen. Met deze vragenlijst proberen wij in kaart te brengen hoe vaak deze klachten zich voordoen en in welke mate ze invloed hebben op het dagelijkse leven van betrokkenen.

De volgende vragen hebben betrekking op deze onaangename gevoelens. Het is de bedoeling dat U elke vraag beantwoordt op de volgende wijze:

Geef aan of u datgene wat vermeld is in de vraag hebt ervaren en, indien dit zo is, in welke mate u hier last van ondervindt op een schaal van 1 tot en met 5. Omcirkel het bij u meest passende antwoord bij de desbetreffende vraag. Het is van groot belang dat alleen waarnemingen van de afgelopen 4 weken worden vermeld en niet van langer geleden.

Waardescore:

1. Als u zich niet gehinderd voelde door of geen last had van het beschreven symptoom, ongemak of de gewaarwording.
2, 3, 4 of 5. Als u in meer of mindere mate zich gehinderd voelt door het beschreven symptoom, ongemak of de gewaarwording (5=meeste last).

---

1. Hebt U in de afgelopen 4 weken last gehad van pijn in de enkels of in de benen en wat was de ernst van deze pijn. *(Omcirkel het meest passende antwoord)*

geen pijn	lichte pijn	matige pijn	erge pijn	intense pijn
1	2	3	4	5

2. Voelde u zich in de afgelopen 4 weken gehinderd in Uw werk of andere activiteiten door Uw beenklachten en in welke mate? *(Omcirkel het meest passende antwoord)*

geen hinder	weinig hinder	matige hinder	erge hinder	zeer erge hinder
1	2	3	4	5

3. Sliep U de afgelopen 4 weken slecht door Uw beenklachten en hoe vaak?
(Omcirkel het meest passende antwoord)

nooit	zelden	vrij vaak	zeer vaak	elke nacht
1	2	3	4	5

In welke mate hebben Uw beenklachten U de afgelopen 4 weken gehinderd bij de onderstaande activiteiten?*(Omcirkel achter ieder item het meest passende antwoord)*

		Geen last	Beetje last	Vrij veel last	Zeer veel last	Gaat gewoon niet
4.	Lang staan	1	2	3	4	5
5.	Traplopen	1	2	3	4	5
6.	Knielen of hurken	1	2	3	4	5
7.	Snel wandelen	1	2	3	4	5
8.	Reizen met tram/bus/ trein/auto/vliegtuig	1	2	3	4	5
9.	Huishoudelijk werk zoals (koken, voor kind zorgen, strijken, schoonmaken)	1	2	3	4	5
10.	Uitgaan naar discotheek, feesten, recepties, e.d.	1	2	3	4	5
11.	Sport en/of zwaar werk	1	2	3	4	5

Klachten aan de benen kunnen tevens invloed hebben op de gemoedstoestand. In welke mate zijn onderstaande zinnen op u van toepassing gedurende de afgelopen vier weken? *(Omcirkel steeds het meest bij Uw situatie passende antwoord)*

		Niet	Beetje	Vrij vaak	Heel vaak	Altijd
12.	Ik voel mij gespannen	1	2	3	4	5
13.	Ik ben snel moe	1	2	3	4	5
14.	Ik heb het gevoel dat ik anderen tot last ben	1	2	3	4	5
15.	Ik moet steeds voorzorgsmaat-regelen nemen, (zoals lang staan vermijden, benen op tijd strekken,benen hoog leggen, elastische kousen dragen, enz.) ombeenklachten te beperken	1	2	3	4	5
16.	Ik schaam me om mijn benen te tonen	1	2	3	4	5
17.	Ik raak snel geïrriteerd	1	2	3	4	5
18.	Ik voel mij gehandicapt	1	2	3	4	5
19.	Ik heb 's ochtends moeite om op gang te komen	1	2	3	4	5
20.	Ik heb geen zin mij onder de mensen te begeven	1	2	3	4	5

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Translation and Validation of the Dutch VEINES-QOL/Sym in Varicose Vein Patients

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ABSTRACT

Objectives: To translate from English to Dutch and evaluate the psychometric properties of the VEnous INsufficiency Epidemiological and Economic Studies (VEINES) questionnaire, divided in symptom (VEINES-Sym) and quality of life (VEINES-QOL) subscales.

Methods: Standard forward–backward translation method was used to translate the 26 items of the VEINES-QOL/Sym. Eligible patients had to complete a standardized questionnaire. Demographic, venous disease characteristics, clinical venous signs, CEAP (clinical, aetiological, anatomical and pathological elements) classification and ultrasound findings were also noted. If item's scores were in an extreme category in more than 70% of patients a floor or ceiling effect was present. Feasibility of the individual items was considered poor if 10% or more of the responses were missing. The validity was tested by comparing the VEINES-QOL/Sym scores to the Short Form 36 (SF-36) scores and across the different 'CEAP' categories. Confirmatory factor analysis was used to assess the underlying structure of the VEINES-QOL/Sym.

Results: Sixty-six patients were included (response rate of 72%). None of the 26 items missed,10% of responses, but two showed ceiling effect. Both the VEINES-QOL and VEINES-Sym showed an excellent internal consistency (Cronbach's alpha of 0.88 and 0.81, respectively). The VEINES-QOL demonstrated a good construct validity for the physical component of the SF-36, but not for the mental component (rho ¼ 0.62 and 0.22, respectively), as expected. The VEINES-Sym correlated poorly to both SF-36's components. According to the confirmatory principle axis factoring, only three out of 25 items did not load sufficiently on the factor.

Conclusions: The Dutch VEINES-QOL/Sym can be used for health-related quality of life research in varicose veins patients and the evaluation of therapies.

INTRODUCTION

Chronic venous disorders (CVD) are defined as the morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/ or signs indicating the need for investigation and/or care.[1] It is a common disease and about 62.1% of females and 49.1% of males in the Western countries are affected with venous symptoms.[2] Most patients affected by CVD experience discomfort and disability in their daily lives which is caused by symptoms such as tingling, aching, burning, pain, muscle cramps, swelling, sensation of throbbing or heaviness, itching skin, restless legs, leg-tiredness and/or fatigue.

Over the last decades much research has been done on measuring health related quality of life (HRQoL) in CVD patients, using generic or disease specific questionnaires. The most commonly used generic instruments in phlebology are the Short Form 36 (SF-36) and the EuroQol (EQ)-5D. Since these measures were developed to be used across many different diseases, it loses precision and sensitivity to change in diseases with specific HRQoL impairment such as varicose veins. Subsequently, disease specific instruments are increasingly used to evaluate the effects of specific treatments in patients with varicose veins.[3-6] To complement the shortcomings of the generic instruments, it is recommended to combine generic and disease specific HRQoL instruments. The available disease specific HRQoL tools focusing on chronic venous insufficiency and/or varicose veins are: Chronic Lower Limb venous Insufficiency (CIVIQ), Aberdeen Varicose Vein Questionnaire (AVVQ) and VEINES-QOL/Sym.[4-6] The AVVQ calculates one global HRQoL score summing symptom and clinical class related items and to a lesser extent HRQoL items.[4] The CIVIQ focuses on HRQoL impairment and includes only one symptom related item. The CIVIQ results in a global score and four separate domain scores (physical, psychological, social impairments and level of pain).[5] The VEnous INsufficiency Epidemiological and Economic Studies (VEINES) questionnaire is positioned in between these two instruments because it balances symptom (VEINES-SYM) and quality of life (VEINES-QOL) items resulting in two separate scores.[6] In our opinion, it is recommended to separate the evaluation of symptoms and HRQoL impairment. The presence and extent of symptoms are likely to correlate well with HRQoL impairment because it is a proxy for disease severity (i.e., construct validity), but symptoms are a different construct than HRQoL and should therefore not be summed in a total score.[7]

Symptom measurement is important and is part of the domain of patient reported outcomes (PRO), but not within the HRQoL construct. Increasingly more clinical trials assessing treatments of varicose veins include improvement of symptoms as an important endpoint in addition to anatomical and HRQoL measures.[8]

The study's objective is to translate and evaluate the psychometric properties of the Dutch translated VEINES-QOL/Sym for patients with varicose veins.

METHODS

Translation and pilot testing

The VEINES-QOL/Sym questionnaire was translated into Dutch by using the recommended forward-backward translation.[9] All translators were asked to place emphasis on conceptual rather than literal equivalence and taking the reading level of a 14years-old in consideration. The forward translations were performed by the principal investigator (SV) and two independent academic dermatologists with special interest in phlebology. The three forward translations were compared, and after consensus was reached, a preliminary common forward-translation was developed. The common forward translation was sent to two English native speakers, who each translated the questionnaire back into English. The backward translations were reviewed by those responsible for the forward translation and an independent dermatologist for conceptual equivalence with the original English version. If necessary, adaption's to the Dutch version were made. Subsequently, the Dutch questionnaire was pilot tested in a heterogeneous group of 20 patients with symptoms and signs of chronic venous disease. Respondents were asked about item difficulty by using a brief questionnaire, but none were encountered during the pilot testing. Therefore, the Dutch VEINES-QOL/Sym was not revised and administered to the study population.

Study subjects

All consecutive patients presenting to the outpatient department of Dermatology with symptoms and objective signs of venous disease, were asked to participate in the study.

Patients were excluded if cosmetic complaints were reported only or if there was no sign of venous disease during physical examination or if no reflux (longer than 0.5s) was found during venous ultrasound examination. Furthermore, patients were excluded if edema was the only clinical sign during physical examination because these patients were more likely to have non-venous causes of edema.

A trained physician examined patient's affected legs that were classified according to the clinical component of the international accepted CEAP classification.[10] Venous signs, such as telangiectasia, reticular veins, varicose veins, edema, skin changes (hyperpigmentation, lipodermatosclerosis) or ulcerations were recorded. Subsequently, ultrasound examination of both the superficial and deep venous systems was performed in standing position.[11] Reflux duration of more than 0.5 seconds was considered as evidence for superficial venous insufficiency.

Questionnaire

After participants provided written informed consent, the Short Form Health Survey (SF-36) and the VEINES- QOL/Sym were completed by the participants. Patients were requested to complete the questionnaires at home and return it by prepaid mail. In case of missing

questionnaire items, patients were contacted by phone in order to retrieve the missing data. If we were not able to reach a patient by phone, missing items were replaced by the median of the completed items reported by an individual for that (sub)scale.

The SF-36 consists of 36 items, divided into 8 different dimension which are summarized in physical (Physical Component Summary [PCS]) and mental (Mental Component Summary [MCS] QOL scores. The MCS and PCS SF-36 scales are scored from 0 to 100, with 0 indicating the least favorable possible health state.[12]

The VEINES-QOL/Sym is a 26-item questionnaire that measures venous symptoms (10 items), time of day leg problems are most intense (1 item), change over the past year (1 item), limitations in daily activities as a result of CVD (9 items) and psychological impact of CVD (5 items) (Figure 1). Two summary scores can be computed; VEINES-Sym score which reflects the extent of venous symptoms and VEINES-QOL score which represents the HRQoL impairment. The item 'time of day your leg problems are most intense' represents descriptive information only, and is therefore not included in the summary score. Higher VEINES-QOL scores indicate a favorable HRQoL (range 0-100).

STATISTICAL ANALYSIS

Feasibility

The feasibility of the questionnaire was evaluated by the overall response rate. Item difficulty was present, if 10% or more of the answers of individual items were missing.

The score distribution of all individual items was evaluated by assessing their floor and ceiling effects (i.e., 70% or more of the respondents exhibited the worst or best possible score). Patients with three or more missing scores were excluded from the analysis, except from the feasibility assessment. Missing values were replaced by the median of the completed items reported by an individual for that (sub)scale.

Structure

Confirmatory factor analysis (CFA) was performed using the principal component in order to test the structure of the VEINES-QOL and VEINES-Sym separately. We forced the analysis to extract one component in order to select the items that loaded convincingly on the component and therefore share the same conceptual meaning. If an item loaded 0.40 or more on the single component it was defined as adequate.[13]

Reliability

Cronbach's alpha (reflecting the internal consistency of an instrument) was tested for the VEINES-Sym and VEINS-QOL separately and were considered good, if between 0.7 and 0.9.

Validity

The construct validity of the VEINES-QOL/Sym (i.e., how it relates to other HRQoL measures) was tested by calculating Spearman's correlation coefficient (rho) between patients' scores and the MCS and PCS of the SF-365. We expected that the VEINES-QOL would correlate well (rho>0.6) and that the VEINES-Sym would correlate moderate (rho>0.3) with the PCS. We hypothesized that both VEINES-QOL and VEINES-Sym would correlate poorly (rho<0.3) with the MCS.

To test the convergent validity of the questionnaire, we assumed that patients with higher level of clinical severity ('C' from the CEAP classification; C1 vs. C2 vs. C3-6) should have a statistically significantly higher impact on HRQOL, which was tested using an analysis of variance (ANOVA).

The distribution of the data were presented as mean with standard deviation (SD) or median with interquartile range (IQR) values as appropriate. Categorical data were analyzed by means of X2 test or, if necessary, Fisher's exact test.

Two sided *P* values of 0.05 or less were considered statistically significant. All analyses were conducted using SPSS (SPSS Inc., Chicago, IL, U.S.A.). The Medical ethical committee of the University Hospital Maastricht (The Netherlands) granted exempt status for this observational study. All participants provided written informed consent.

RESULTS

Study population

Of the eligible 94 patients with symptoms and objective signs of venous disease who were invited to participate in this study, 68 patients (response rate 72%) completed the questionnaire. Two patients were excluded because of incomplete questionnaires (2.9%). Of the 66 participants, 73% were women and the mean age of the study population was 54.9 years (SD 13.1, range 20- 81 years; Table I). Classified according to the C-component of CEAP classification, 35 % of the participants were classified in 'C1', 33% in 'C2' and 32% in 'C3-C6'.

Feasibility

None of the individual items were considered suboptimal as missing responses varied between 0% and 4.6%. However, item 1.9 ('tingling sensation') and item 4b ('daily activities at home') were both missing in 4.6% of the participants, suggesting borderline feasibility of these items.

From the 25 items in the questionnaire, 2 demonstrated a substantial ceiling effect with 75.8% and 75.8% of the respondents indicating the highest score for item 5a ('cut down the amount of time you spent on work or other activities') and item 8c ('have you felt a burden to your family or friend').

Table I: Patient characteristics.

Characteristics	No. of patients (%)
Sex	17 males (26%)
	49 females (73%)
Age, mean (SD, range)	54.89 (13.06, years 20-81)
CEAP classification	
C1	23 (35%)
C2	22 (33%)
C3	17 (26%)
C4	3 (4.5%)
C5	0
C6	1 (1.5%)
Perforating veins	0
Deep system (femoral vein)	2 (3%)
No reflux	19 (29%)
Reflux	47 (71%)

STRUCTURE

VEINES-Sym

All nine VEINES- Sym items loaded higher than the cuff-off value of 0.40, suggesting these items fit the unidimensional structure of the VEINES-Sym. The loadings varied between 0.46 and 0.710 (Table II).

VEINES-QOL /Sym

Twenty one out of 25 items loaded higher than the cutoff value of 0.40 and were therefore assigned to the component. The loadings varied between 0.41 and 0.79. Only two items (item 3 'compared to one year ago, how would you rate your leg problem in general now' and 8a 'have you felt concerned about the appearance of your leg(s)') showed item complexity with a loading of 0.31 and 0.289 respectively, suggesting these items do not fit the unidimensional structure of the VEINES-QOL/Sym. Item 1.8 'during the past four weeks how often have you had itching legs', item 1.3 'during the past four weeks how often have you had swollen legs' and item 8e 'during the past four weeks how often has the appearance of your leg(s) influenced your choice of clothing' were borderline complex with a loading of 0.40, 0.38 and 0.35 respectively.

RELIABILITY

The item responses of the VEINES-QOL and VEINES-Sym showed an excellent internal consistency (Cronbach's alpha of 0.88 and 0.81 respectively).

Table II: The loadings* of a confirmatory primary component analysis, for VEINES-Sym and VEINES-Sym/QOL separately.

Items		VEINES-Sym	VEINES-Sym/QOL
1.1	Heavy legs	.61	.54
1.2	Aching legs	.73	.59
1.3	Swelling	.46	.38
1.4	Night cramps	.49	.43
1.5	Burning	.64	.52
1.6	Restless legs	.65	.50
1.7	Throbbing	.63	.58
1.8	Itching	.46	.40
1.9	Tingling	.68	.55
7	Pain	.71	.62
3	Evolution of the leg problem	.31	
4a	Limitation of activities at work	.56	
4b	Limitation of activities at home	.79	
4c	Limitation of standing activities	.68	
4d	Limitation of sitting activities	.66	
5a	Less time spent on work or activities	.75	
5b	Accomplished less	.76	
5c	Limited in the kind of work or activities	.56	
5d	Difficulty performing the work or activities	.67	
6	Social activities	.77	
8a	Concerned about appearance of the legs	.29	
8b	Felt irritable	.66	
8c	Felt a burden to your family of friends	.55	
8d	Worried about bumping the legs	.41	
8e	Choice of clothing	.35	

* Loadings >0.40 are included, indicating these items loaded on the expected scale (VEINES-Sym and VEINESSym/QOL separately).

Validity

The VEINES-Sym is borderline moderately correlated with the physical component and poorly with the mental component of the SF-36 (rho =0.4 and rho=0.1 respectively). As expected, the VEINES-QOL is strongly correlated with the physical component and poorly correlated with the mental component of the SF-36 (rho =0.6 and rho=0.2 respectively) confirming the convergent validity of the instrument.

In contrast to our hypothesis, the median scores of both the VEINES-Sym and VEINES-QOL were not affected significantly by severity of varicose veins (C1, C2, C3-C6; p=0.80 and p=0.41 respectively) and varied between 48- 52 and 48-53 respectively. This observation may indicate a poor construct validity of the instrument.

DISCUSSION

In this study, we translated and evaluated the psychometric properties of the Dutch translated VEINES-QOL/Sym in patients with varicose veins. This venous specific health related quality of life and symptom instrument showed a good acceptability, validity and high reliability. This study provided evidence for a high feasibility, since 24 out of 26 items showed no floor or ceiling effects which indicates a good discriminative effect of the items. The high construct validity was supported by the strong correlation between the VEINES-QOL and the physical component of the SF-36.

Interestingly, correlations between the VEINES-QOL and the SF-36 are higher for the physical rather than for the mental scores suggesting that the psychosocial impact of varicose veins is more in the functioning domain[7]. This correlation with functioning is in line with the study's of the original English and French VEINES-QOL/Sym versions and validation studies of the AVVQ and the CIVIQ instruments.[6,14-15] As expected, the VEINES- Sym score is not correlated to the SF-36. This correlates with the original version.[6] We therefore suggest that the symptoms construct differs from the mental and physical components (e.a impairment, disability, functioning). However, all three belong to the measurement of HRQoL.[16-18]

We were not able to achieve significant differences between the clinical 'C'EAP categories. The poor correlation between the VEINES-Sym and VEINS-QOL scores and the CEAP classification may be explained by study population (excluding edema patients), small sample size of patients with severe venous disease, suboptimal measure of disease severity and/or poor construct validity of the VEINES instrument. In a predominantly C1-3 population, venous disease may have induced limited HRQoL impairment, but is accompanied by the presence of symptoms.

In the confirmatory Principle Axis Factoring (PAF) 21 out of 25 items did load sufficiently on the factor, indicating a good unidimensional underlying construct of these findings. However, the construct validity of the items would suggest separate scales for symptoms (items 1, 3, 7), functioning (items 4, 5, 6) and psychological aspects (item 8). A preliminary exploratory PAF confirmed these scales partly (data not shown). Moreover, it was not the objective of this study to refine the current instrument.

As we mentioned above, the present study showed a high acceptability. We reported that two items showed a substantial ceiling effect, including 'cut down the amount of time you spent on work or other activities' and 'have you felt a burden to your family or friend'. Not surprisingly, both non-discriminative items are mental aspects of the VEINES-QOL/Sym.

Therefore, it is questionable whether the mental items are specific enough for patients affected with predominantly mild varicose veins. In this study population, mental health appears to be less impaired compared to physical health, which is in contrast to the results of other studies showing that varicose veins may have an impact on the mental health.[19]

A limitation of the current study is the relatively small group of patients with severe venous disease. The response rate was adequate, but this study was restricted to patients visiting a academic center potentially limiting the generalization of our findings. Future psychometric studies need to confirm the responsiveness (i.e., sensitivity to change) and minimal clinical important difference of the VEINES-QOL/Sym.

In conclusion, we showed that the psychometric properties of the Dutch VEINESQOL/Sym were comparable to the original English version. This supports applications of the Dutch VEINES-QOL/Sym during HRQoL research in the Dutch varicose veins population.

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Chapter 4

Comparing Endovenous Laser Ablation, Foam Sclerotherapy and Conventional Surgery for Great Saphenous Varicose Veins

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ABSTRACT

Background: Many case-series have been published on treatments of varicose veins, but comparative randomized controlled trials remain sparse.

Objective: to compare the anatomical success rate, frequency of major complications and quality of life improvement of endovenous laser ablation (EVLA), ultrasound-guided foam sclerotherapy (UGFS) and conventional surgery (CS), after one year follow-up.

Methods: 240 consecutive patients with primary symptomatic great saphenous vein reflux were randomized to endovenous laser ablation, ultrasound-guided foam sclerotherapy or conventional surgery, consisting of high ligation and short stripping. Primary outcome was anatomical success defined as obliteration or absence of the treated vein on ultrasound examination after one year. Secondary outcomes were complications, improvement of the 'C' class of the CEAP classification and improvement of disease specific (CIVIQ) and general (EQ5D) quality of life scores.

Results: More than 80% of the study population was classified as C2 or C3 venous disease. After one year, the anatomical success rate was highest after EVLA (88.5%), followed by CS (88.2%) and UGFS (72.2%) (P<.001). The complication rate was low and comparable between treatment groups. All groups showed significant (p<0.001) improvement of EQ5D and CIVIQ scores after therapy. 84.3% of all treated patients showed an improvement of the 'C' of the CEAP classification.

Conclusion: After one year follow up EVLA is as effective as CS and superior to UGFS according to occlusion on ultrasound duplex. Quality of life improves after treatment in all groups significantly.

Registration number: NCT00529672

INTRODUCTION

Varicose veins of the legs affect approximately 25% of the population[1] and may have a substantial impact on patient's health-related quality of life (HRQoL). The treatment of varicose veins and its complications consume a relatively large proportion of the limited health care resources.[1,2]

Until recently, conventional surgery (CS) of the great saphenous vein (GSV), consisting of high ligation at the saphenofemoral junction (SFJ) and stripping of the above knee GSV, was the standard of care. In the last decade, minimally invasive techniques such as endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and ultrasound-guided foam sclerotherapy (UGFS) have challenged the position of CS for primary varicose veins.[3] These techniques are effective (occlusion rates of EVLA and RFA >90%), and safe.[4,5] CS associates stripping of the refluxing GSV trunk with high ligation at the SFJ and this may induce neovascularization.[6,7,8] Endovenous treatment techniques are performed without high ligation, which may be an advantage. Additional advantages of EVLA, RFA and UGFS over CS are that they can be easily performed in an ambulatory setting. A comparative meta-analysis of observational studies and randomized clinical trials (RCTs) demonstrated that both EVLA and RFA were superior to CS and UGFS.[5] In the last few years several important RCTs comparing two different treatment modalities for varicose veins show that the minimally invasive techniques are at least as effective as CS, and that they result in faster recovery time, less post-operative pain, and that they are preferred by patients. [7,9,10,11] In 2011, Rasmussen et al were the first to compare more than two different treatments in a 4-arm RCT.[12] This study showed that thermal ablation and CS, all performed under tumescent anesthesia, had anatomical results than UGFS however patient reported outcomes were better after in the UGFS and RFA.

A recent comparative study of UGFS and CS showed significantly higher efficacy rates two years after CS. However, there were no differences in patient-reported outcomes.[13]

The objective of this study is to compare the anatomical success rate, frequency of complications, and HRQoL improvement of EVLA, UGFS, and CS for the treatment of primary incompetent GSV after one year.

METHODS

Our study was designed as a consecutive single center RCT at the department of dermatology and vascular surgery of Erasmus Medical Center Rotterdam, The Netherlands, starting in January 2007. Due to a decreasing inclusion rate, the same departments of Catharina Hospital Eindhoven were added as second center in May 2009. The last patient was treated in May 2010. The medical ethical committee of Erasmus MC Rotterdam approved our protocol. (MEC2005-325).

In Latin, the GSV is called "Vena Saphena Magna" and in the Netherlands we use this name to indicate the GSV; therefore we have chosen to call our study the MAGNA trial.

Adult patients with a symptomatic primary incompetent GSV at least above the knee with a diameter of ≥0.5 cm and with an incompetent saphenofemoral junction were eligible to participate. The incompetence of the GSV was defined as reflux of ≥0.5 seconds at color duplex ultrasound (Philips, HDI 4500, 10MHz probe). Exclusion criteria were previous treatment of the ipsilateral GSV, deep venous incompetence or obstruction, agenesis of the deep system, vascular malformations, use of anticoagulation, pregnancy, heart failure, contraindication for one of the treatments, (e.g., allergy for aethoxysclerol or lidocaine), immobility, arterial insufficiency (defined as an Ankle-Brachial Index less than 0.6), age under 18 years, and inability to provide written informed consent to trial participation.

Treatment

In this study only the GSV in the thigh (from just below or above knee level in most cases) was treated. Patients were allocated to one of the three treatments. After written informed consent, eligible patients were randomized using a computerized list by an independent research nurse. All treatments were performed by dermatologists or surgeons with more than 5 years of experience with the treatments (EVLA and UGFS, and CS and EVLA, respectively).

Endovenous laser ablation

EVLA was performed under ultrasound guidance with a 940 nm diode laser as previously described.[14] In brief, venous access was obtained by puncturing the vein at knee level, with a 16 or 18 French needle under ultrasound guidance. After entrance to the varicose vein was established, a guide wire was passed through the hollow needle into the vein up to the level of the saphenofemoral junction (SFJ). The needle was removed and a small cutaneous incision of 3 mm was made, then an introducer sheath was passed over the guide wire and positioned 1-2 centimeters below the SFJ. Subsequently, the laser fiber was introduced after removing the guide wire. About 250-500 ml (depending on the length of treated vein) of tumescent anesthesic solution was administered into the saphenous compartment under ultrasound guidance using a mechanical infusion pump. Withdrawal of the laser fiber was performed in continuous mode and it was attempted to deliver at least 60 J/cm.[15]

Ultrasound-guided Foam Sclerotherapy

Ultrasound-guided foam sclerotherapy was performed as reported previously.[14]

The Tessari-method[16] was used to prepare foam (1 cc aethoxysclerol 3%: 3cc air), which was injected directly under ultrasound guidance in the GSV with the patient in horizontal position.[14,16] The volume of injected foam depended on the length and diameter of the vessel, with a maximum of 10mL per session (as suggested by the 2nd European Consensus).[17] After injection, the patient remained horizontally for at least 5 minutes. If considered necessary, UGFS of the included GSV could be repeated after three months.

Conventional surgery

High ligation with short (above knee) stripping was performed under spinal or general anesthesia. Flush SFJ ligation was followed by ligation of all tributaries back to the second branch and invaginating stripping of the GSV to knee level. The cribriform fascia, superficial fascia and skin were closed.

After all treatments ambulatory compressive bandage was applied for 48 hours, followed by therapeutic compression stockings for 2 weeks post procedure. All patients were observed for at least half an hour in the clinic after treatment. No specific analgesics were prescribed. Patients were encouraged to mobilize and to resume their usual activities as soon as possible.

Outcomes

Primary outcome

Patients were evaluated at 3 and 12 months for clinical examination and duplex ultrasound. The primary outcome was anatomical success according to duplex ultrasound evaluation. For EVLA and UGFS this was defined as complete obliteration, without flow or reflux, of the GSV at the level of the mid-thigh. For CS success was defined as absence of the GSV in the saphenous compartment at thigh level. We differentiated between obliteration, partial or complete patency of the treated vein, with or without reflux.

Postoperative neovascularization was assessed at the level of the SFJ using the classification described by De Maeseneer et al, 'The degree of neovascularization was determined as 'grade 1 neovascularization' (tiny new vein(s) up to 3 mm diameter, not connecting with any superficial vein) and 'grade 2 neovascularization' (tortuous new vein(s) with a diameter ≥4 mm, with pathological reflux and connecting with thigh varicose veins)'.[18]

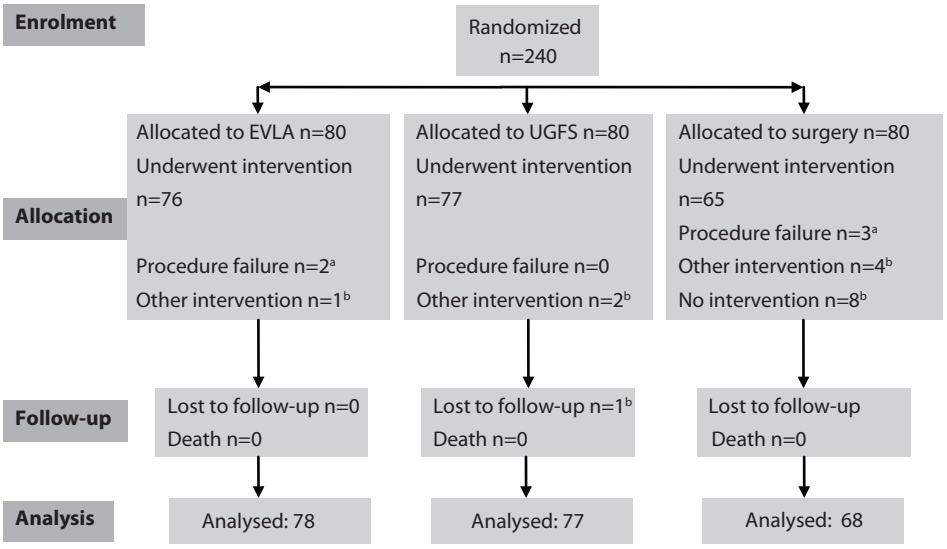
Secondary outcomes

At all visits the 'C' of the CEAP classification was recorded. The basic CEAP classification as described by Eklöf was used, which means patients are classified according to their highest C score.[19] The type and frequency of complications of the different treatments were reported. The following complications were assessed: superficial vein thrombosis (related to site of treatment), hyperpigmentation (at treatment site), paresthesia (defined as abnormal skin sensations such as tingling, tickling, itching, burning or numbness), scotoma, migraine, skin burns, skin necrosis, anaphylactic shock, wound infection for which antibiotic therapy was needed, symptomatic deep venous thrombosis (DVT), based on history and confirmed by duplex examination, and symptomatic pulmonary embolism.

The effect of the treatment on HRQoL was assessed using the disease specific Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ)[20] and the generic EuroQol 5D instrument (EQ-5D)[21] questionnaire. Additional phlebectomies were permitted during CS or EVLA or (in case of residual superficial varicose veins) at three months postoperative. UGFS

could be used as an 'escape' therapy in case of failure of the initially allocated treatment of the GSV.

Figure 1: Consort flow.



[a] If there was a procedure failure, patients were treated with UGFS, data analysis was on a intention to treat basis.
[b] Patients who did not receive treatment or received another treatment or were lost of follow up in the first year were excluded from the analysis.

Statistical analysis

Sample size calculation indicated that 240 legs (80 in each group) were needed to detect a significant difference of 0.05 in anatomical success rate between the three groups with a beta of 0.20. (i.e. power=80%) Data were analyzed on an intention to treat basis. Continuous data were first tested for normality using One-Sample Kolmogorov-Smirnov Test. For normal distribution, data were presented as means with standard deviation (SD) and analysis with one way ANOVA was done to compare it across three treatment groups.

Categorical data were analyzed by means of χ^2 test or, if appropriate, Fisher's exact test. Patients with bilateral GSV insufficiency were randomized separately for each leg. For efficacy analysis, both GSVs were included, but for HRQoL analyses these patients were excluded because patients are unable to differentiate the impact of varicose veins of each leg on HRQoL.[22]

A generalized estimating equation (GEE) model with a logit link was used to model the odds ratio for total occlusion over time. To take the correlation into account between two

legs of the same patient and multiple measurements over time, we chose an unstructured covariance matrix and use the patients as the independent subjects. For EQ5D, Civiq, Health and CEAP outcomes, we used a linear mixed model (LMM) with empirical standard errors. For this model we chose a direct product of an unstructured covariance matrix (for the covariance within a leg) and a compound symmetry correlation matrix (for the correlations within a patient between the legs). Thereby we allow for an unstructured correlation matrix between measurements over time within one leg and we assume that the unstructured correlation matrix is equal for the first and the second leg within one person.

Statistical analysis was performed using SPSS® version 20.0 (SPSS, Chicago, Illinois, USA) and SAS 9.2 (SAS institute Inc., Cary, NC, USA). All statistical tests were two-sided and considered significant at the P<.05 level.

RESULTS

Study population

In 223 eligible patients, 240 legs were randomized for one of the treatments between January 2007 and December 2009 (Figure 1). Seventeen patients were excluded from the analysis; 16 did not fulfill the inclusion criteria and 1 was lost to follow up.

Five patients were treated with UGFS because initial treatment had failed; two patients from the EVLA group and three patients from the CS group. Data was analyzed on an 'intention to treat' basis, according to randomization. 'As treated analysis' showed no significant difference. In the study population, 82.3% suffered C2 and/or C3 venous insufficiency. The groups were well matched for the demographic data, CEAP classification and GSV diameter and HRQoL impairment (Table I). The patients in the EVLA group were significantly younger than those in the CS and UGFS group. Patients in the EVLA group received on average 59.16 J/cm (SD 15.20). Patients in the UGFS group received a mean of 4.7cc (SD 1.19) foam. The majority of patients were treated in one session of UGFS. Six patients with lasting complaints received a second treatment within the first year.

Anatomical success

EVLA and surgery were comparably effective (88.5%, n 69; 88,2%, n 60 respectively), after one year follow up (Figure 2, Table II) However, in the CS group 10% (n 7) of patients had grade 1 neovascularization at ultrasound examination of the groin. After one year the occlusion rate of UGFS was 72,7% (n 56) which was significantly lower than EVLA and CS (P<.02). Twenty-one patients (27.3%) of the UGFS group had partial obliteration with reflux. In 11 of these patients initial treatment resulted in complete relief of complaints despite persisting reflux after one year follow up and therefore they did not undergo any additional treatment.

Figure 2: Occlusion after 12 months. Complete obliteration after 12 months. The proportion of legs that had complete obliteration or absence of the GSV after treatment was significantly different between EVLA, UGFS and CS. (P<.02)

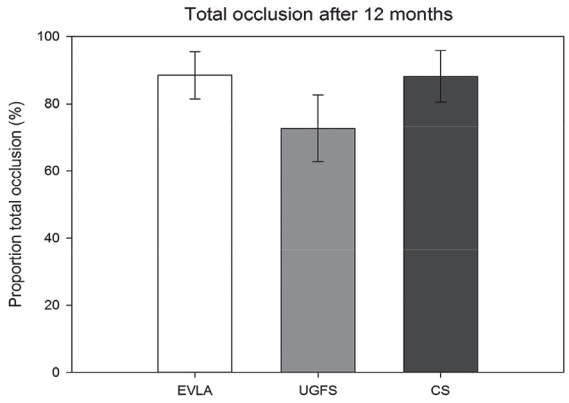


Table I: The distribution of baseline characteristics for each of the three treatment groups.

	EVLA N=78	**UGFS N=77**	**CS N=68**	**p-value**
Age, years (SD)	49 (15.03)	56 (13.30)	52 (15.59)	0.005[a]
Sex n, (%)				
Women	54 (69.2)	52 (67.5)	46 (67.6)	0.89[b]
Men	24 (30.8)	25 (32.5)	22 (32.4)	
Side n, (%)				
Left	48 (61.5)	45 (58.4)	34 (50)	0.36[b]
Right	30 (38.5)	32 (41.6)	34 (50)	
Unilateral n, (%)	62 (79.5)	58 (75.3)	51 (75)	0.74[b]
Bilateral (same treatment)	6 (7.7)	11 (14.3)	8 (11.7)	
Bilateral (different treatment)	10 (12.8)	8 (10.4)	9 (13.3)	
Mean GSV diameter				
Left, cm (SD)	0.64 (0.15)	0.58 (0.14)	0.62 (0.14)	0.08[a]
Right, cm (SD)	0.59 (0.11)	0.62 (0.14)	0.59(0.16)	0.65[a]
CEAP n, (%)				
C1	0	0	0	0.64[c]
C2	37 (47.4)	33 (42.9)	28 (41.2)	
C3	29 (37.2)	30 (39.0)	21 (30.9)	
C4	8 (10.3)	8 (10.4)	14 (20.6)	
C5	0	1 (1.3)	1 (1.5)	
C6	0	0	0	
Unknown	4 (5.1)	5 (6.5)	4 (5.8)	

	EVLA N=78	UGFS N=77	CS N=68	p-value
CIVIQ				
Mean score (SD)	25.21 (20.73)	23.96 (17.97)	25.13 (19.15)	0.91[a]
EQ-5D				
Mean score (SD)	0.85 (0.16)	0.83 (0.20)	0.86 (0.11)	0.65[a]
General health score %, (SD)	79.4% (14.6)	78.8% (12.5)	79.1% (12.7)	0.96[a]

Abbreviations: IQR, interquartal range; SD, standard deviation; cm, centimetres.
[a] Anova
[b] Chi square
[c] Fisher exact

Table II: Repeated measurement analyses for all outcome measures.

	N	CS	EVLA		UGFS		
			OR for total occlusion	95% CI	OR for total occlusion	95% CI	p-value
Anatomical Succes							
Occlusion	223						
Unadjusted[a]		Reference	1.24	(0.56-2.77)	0.34	(0.17-0.67)	0.02
Adjusted[a,b]		Reference	1.22	(0.55-2.69)	0.35	(0.17-0.67)	0.02
	N		**Difference Mean change in score**	**95% CI**	**Difference Mean change in score**	**95% CI**	**p-value**
CEAP							
C-score	210[d]						
Unadjusted[c]		Reference	0.00	(-0.24-0.24)	0.09	(-0.14-0.33)	0.61
Adjusted[c.b]		Reference	0.00	(-0.24-0.24)	0.10	(-0.12-0.33)	0.55
Quality of Life							
CIVIQ	185[e]						
Unadjusted[c]		Reference	-2.01	(-6.43-2.41)	-0.63	(-4.91-3.65)	0.63
Adjusted[c.b]		Reference	-1.93	(-6.36-2.49)	-0.66	(-4.89-3.57)	0.67
EQ5D	175[f]						
Unadjusted[c]		Reference	0.01	(-0.02-0.04)	0.01	(-0.03-0.04)	0.86
Adjusted[c.b]		Reference	0.01	(-0.02-0.04)	0.01	(-0.02-0.04)	0.81
Health	175[f]						
Unadjusted[c]		Reference	1.73	(-1.55-5.01)	-2.03	(-4.79-0.73)	0.04
Adjusted[c.b]		Reference	1.61	(-1.67-4.89)	-1.97	(-4.78-0.84)	0.07

Abbreviations: OR, odds ratio; N, number;
[a] time since randomization was included in the model
[b] adjusted for age and sex
[c] time since randomization and baseline score were included in the model
[d] 13 patients with missing CEAP scores at all time points were excluded.
[e] 14 patients with missing CIVIQ scores and 24 patient with different bilateral randomized treatment were excluded
[f] 24 patients with missing EQ5D/Health scores and 24 patients with different bilateral randomized treatment were excluded

Clinical Improvement

In all groups the C of the CEAP-classification decreased significantly after treatment, and there was no difference between groups. An improvement of the C score was seen in 79.4% of all treated patients at 3 months (Figure 3). After 12 months 47.6% of all patients showed improvement of at least 2 catogories (Table III). However the mean improvement in C-score was not significantly different between the three groups. (Table II) The clinical situation according to the CEAP deteriorated in one patient treated with EVLA; he developed hyper pigmentation at the treatment site and ankle after treatment.

Table III: Changes in 'C' from CEAP classification 12 months after therapy.

		C-improvement					
		-3.00	**-2.00**	**-1.00**	**0**	**2.00**	**Total**
Type of Treatment (%)	EVLA	10 (13.5)	26 (35.1)	25 (33.8)	12 (16.2)	1 (0.4)	74
	UGFS	7 (9.7)	22 (30.6)	33 (45.8)	10 (13.9)	0	72
	CS	8 (12.5)	27 (42.2)	19 (29.7)	10 (15.6)	0	64
Total		25 (11.9)	75 (35.7)	77 (36.7)	32 (15.2)	1 (0.48)	210

Abbreviations: EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy; CS, conventional surgery

Complications

Complications were recorded in the first year after initial treatment (Table IV). The frequency of adverse events was low and not significantly different between the three treatment groups (P=.64). Ten patients were seen earlier than 3 months after treatment with complaints of pain. All these patients had a superficial vein thrombosis of a tributary of the GSV and duplex ultrasound excluded additional DVT in all cases. No symptomatic DVT, PE or scotoma occurred. No procedure related mortality was observed. Three patients received antibiotics because of wound infection in the groin after CS, there were no wound infections after EVLA nor after UGFS (P=.023). Most of the milder adverse events were transient, and disappeared after 3 months. Overall, 11 CS, 7 EVLA and 5 UGFS patients reported any adverse events.

Quality of life

Seventeen patients with bilateral GSV insufficiency were excluded from all QoL analysis. Eight of these patients were allocated for the same treatment in both legs and 9 patients for different treatments. The CIVIQ and EQ5D score improved in all groups at 3 months and remained relatively stable until 1 year (Figure 3b, 3c, 3d) Civiq score and EQ5D showed no significant differences between the three groups. Additional analysis adjusted for age and sex showed no significant differences for Civiq, EQ5D and health score (Table II).

It is remarkable that the CIVIQ scores improved in 11 patients (14%) of the UGFS group despite their remaining (segmental) reflux on ultrasound examination and without performing additional injections.

Table IV: Distribution of the complications for each of the three therapies at 3 and 12 months after therapy.

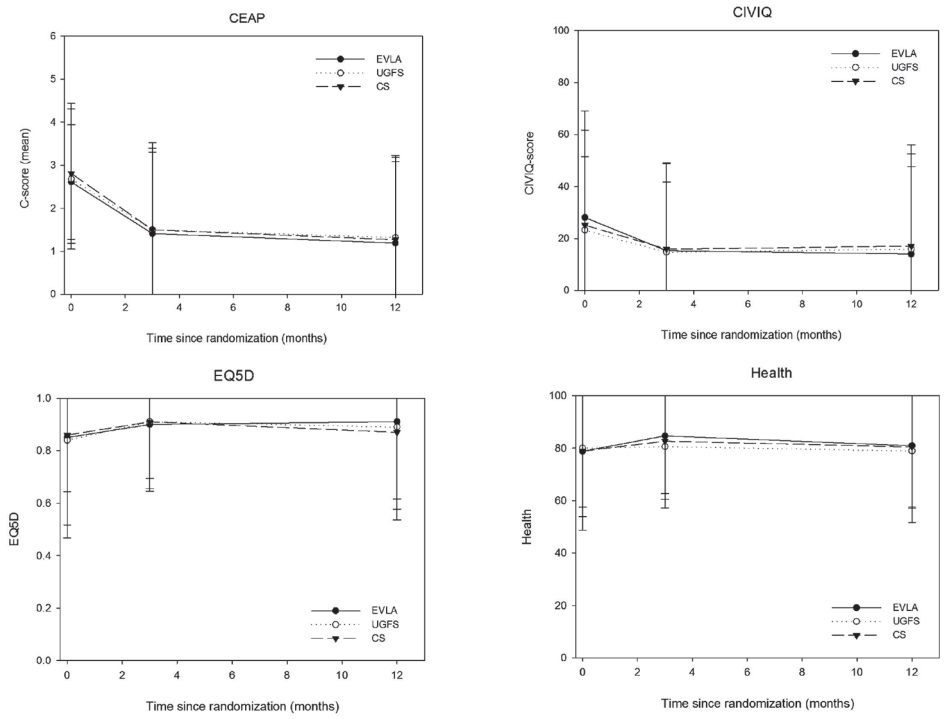
	EVLA N=78	UGFS N=77	CS N=68	p-value[a]
3 months				
Hyperpigmentation	2	1	0	0.78
Paresthesia	2	1	4	0.30
Superficial vein thrombosis	3	3	4	0.85
Wound infection[b]	0	0	3	0.03
Deep vein thrombosis	0	0	0	1.00
Pulmonary emboli	0	0	0	1.00
Death due to therapy	0	0	0	1.00
Total number of patients with complications	7	5	11	0.64
12 months				
Hyperpigmentation	1	1	0	1.00
Paresthesia	0	1	1	1.00

[a] Fisher exact
[b] requiring systemic antibiotics

Additional Interventions

Phlebectomies were permitted during initial treatment with the intention of removing all varicosities in the same procedure, but because of practical issues this was not possible in all cases. In 15 patients (19.2%) in the EVLA group and 18 (25.7%) in the CS group phlebectomy was performed during initial treatment. In 12 (15.3%), 15 (19.5%) and 11 (15.7%) of the EVLA, UGFS and CS group respectively, phlebectomies were performed after three months. In the UGFS group 6 patients (4.6%) with lasting reflux and complaints received a second injection with foam.

Figure 3: Repeated Measurements. **(A**) Repeated measurement analysis for CEAP and quality-of-life scores, thirteen patients with missing CEAP scores were excluded. (**B**) Fourteen patients with missing Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) scores and 24 patients with different bilateral randomized treatment were excluded. (**C** and **D**) Twenty-four patients with missing EuroQol 5D (EQ-5D)/health scores and 24 patients with different bilateral randomized treatment were excluded.



CS, Conventional surgery; EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy.

Subgroup analysis

Subgroup analysis did not show any significant differences between anatomical success, clinical improvement, complications, or quality of life improvements between the two centers. There were no significant differences of CIVIQ and EQ-5D scores between unilateral and bilateral treatments (n=52) nor between groups with or without additional treatments.

There were no significant differences in anatomical success, CEAP classification or HRQoL scores between patients who received additional treatments and those who did not. The group that received additional treatments reported more adverse events than the patients who had only GSV treatment (12.7% versus 6.7%).

DISCUSSION

In the last decade, EVLA and RFA were introduced and UGFS has been optimized. These minimal invasive interventions are increasingly used as alternative to CS for treating saphenous veins.[4,5] The MAGNA trial shows that EVLA and CS are comparably effective (almost 90%) and that both are significantly more effective than UGFS (72.7%) using ultrasound based anatomical outcomes. Complications are rare and quality of life (CIVIQ and EQ5D) improved significantly after each treatment. The results of this RCT are strikingly similar to other clinical studies, meta-analysis and two recent RCTs that included UGFS increasing the validity of the findings .[5,12,13,23] One year after treatment, remaining (segmental) flow with reflux was observed in more than a quarter of the patients treated with UGFS, which is in line with other observational studies and RCTs.[12,13,24,25] Neovascularization occurs in 10% of the patients in the CS group one year post operatively, which corresponds with results of a previous study focusing on the effect of closing the cribriform fascia to contain postoperative neovascularization at the SFJ.[18] In contrast to the significant improvement of the CIVIQ, the generic scores of the EQ-5D improved slightly, suggesting that either saphenous varicose veins have a mild impact on the global HRQoL, this instrument lacks content validity to assess impact of venous disease in C2-C3 patients and/or the sensitivity to change the EQ-5D is limited in patients with venous disease. However, other clinical studies did observe improvement in the SF-36 and the EQ-5D, which may be explained by study population (82% of patients were C2-3 venous disease), timing of assessment after therapy (3 months and one year), or limited sample size of this study.[12,26] Applying the Norman's rule of thumb on the unadjusted data, none of the improvements in the CIVIQ and EQ-5D appeared to be clinically relevant.[27]

Despite randomization EVLA treated patients were significantly younger than those in the other two treatment arms. Adjusting for age and sex in a logistic model, there were no differences in CIVIQ scores or in CEAP classification between the three groups.

In accordance with other RCTs comparing CS to new minimally invasive treatment methods, we had difficulty enrolling the required number of patients in the RCT because of the reluctance among patients to undergo CS. Therefore, an additional center was added during the study period, but no differences in outcomes were noted between the two centers. Of the seventeen included patients that withdrew from the trial, ten were assigned to CS suggesting that informed patients preferred minimally invasive treatments.

The primary outcome of this study was total occlusion and/or absence of the treated GSV according to ultrasound. This outcome has the advantage to be objective and reproducible and is possible a proxy of symptom reduction and future clinical relevant recurrence. These latter assumptions will be tested when the 5-year results become available. Also, defining the outcome as total occlusion may have been too strict, because 'remodeling' of the insufficient vein, as is often seen after UGFS may be associated with alleviation of symptoms while persisting flow with or without reflux is present in the treated vein. Eleven patients with residual reflux

after UGFS did decline an additional UGFS session because absence of venous symptoms. This observation challenges the strict definition of primary outcome criteria such as 'total occlusion' and 'absence of reflux' used as the gold standard for evaluation after GSV treatment in RCTs. Moreover, it emphasizes the conviction that we treat patients and not ultrasound findings.[28]

Recently, the Union Internationale de Phlébologie has proposed a new classification to describe the fate of the junction and the treated trunk after endovenous ablation.[29] This classification allows to describe postoperative findings more detailed, distinguishing between obliteration, partial or complete patency of the treated vein, and segmental obliteration or patency of the treated trunk, with or without reflux. Apart from these duplex ultrasound findings, clinical outcome parameters as well as other outcome measures such as patient-reported outcomes (e.g., HRQoL, symptoms, satisfaction and preference) should be considered.[13,29,30] In contrast to HRQoL, symptom reduction was not maximally assessed in this study, which in retrospect is a missed opportunity.[13] At time of the study design, we overlooked the problem of including bilateral GSV. For the HRQoL outcomes, patients with two different study treatments were excluded from the HRQoL analysis, because patients may not differentiate HRQoL impairment between both legs. Patients with the same treatment for both legs were included for HRQoL analysis by taking the correlation between HRQoL scores of the same patient into account. All patients were included in the efficacy analysis, which was adjustment for bilateral GSV treatments.

Because of the scarring after CS and in a lesser extent EVLA having a blinded outcome assessor was not feasible. The ultrasound investigations were done by physicians not necessarily part of the research team, hopefully limiting the impact of this limitation.

In this study, phlebectomies were allowed during initial treatment of the study GSV in patients allocated to EVLA or CS or after 3 months for all included patients. Phlebectomies were proposed to all study patients with residual superficial varicose veins as additional treatment after three months irrespective of the study treatment. The MAGNA trial includes the three treatments most frequently used in The Netherlands in 2007 explaining the exclusion of segmental RFA. In this study, CS was performed using spinal or general anesthesia, which is still common practice in the Netherlands. Hopefully the long-term results of the minimal invasive interventions will stimulate surgeons to switch to minimally invasive procedures and/or use tumescent anesthesia when CS is indicated.[28] Using tumescent instead of general anesthesia will improve patient satisfaction and will lead to shorter down time after intervention.[31] The five year follow-up of the MAGNA trial and other similar ongoing RCT's will further clarify whether the observed results of EVLA, UGFS and CS persist over time.

Conclusion

The one-year results of the MAGNA trial show that the short term efficacy, defined as anatomical success according to duplex ultrasound, is equally high for EVLA and CS and lower for UGFS. The treatments are equally safe, no severe adverse events were seen. Wound infections and neovascularization were more common after CS. All therapies resulted in significant clinical and HRQoL improvement. Long-term efficacy of these three intervention methods needs to be established and will be available in four years.

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Chapter 5

The Effect of Single Phlebectomies of Tributary on Great Saphenous Vein Reflux

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ABSTRACT

Background: Phlebectomy of varicose tributaries is usually considered an additional treatment after or during saphenous ablation. As phlebectomies alone affect the hemodynamics of the venous system, this treatment can be effective as primary intervention in selected patients.

Objective: To analyze hemodynamic, clinical and patient reported outcomes after phlebectomies in a prospective multicentre study and to determine predictors for treatment success (restoring GSV competence).

Methods: Patients with symptomatic great saphenous vein (GSV) and tributary incompetence (reflux >0.5 s) at the level of the thigh were included. Duplex ultrasound (DUS) was used to assess GSV and tributary characteristics, and a reflux-elimination test was performed. Three and twelve months after phlebectomy of the tributary, reflux and GSV diameter were evaluated with DUS. Clinical outcome measures were C of the CEAP classification and Venous Clinical Severity Score (VCSS); patients' reported outcome was determined by the Aberdeen Varicose Vein Questionnaire (AVVQ). To evaluate differences between the success and failure groups, baseline DUS characteristics, VCSS, CEAP and AVVQ were compared. Multivariable logistic regression, including all clinically relevant variables following a backward variable elimination process was used to determine predictors for success. The model was internally validated using 1000 bootstrap samples.

Results: 94 patients (65 women, 29 men) with a mean age of 53 years were included. The majority had C2 or C3 disease. One year after treatment, GSV reflux had disappeared in 50% of patients (P<.01), and GSV diameter had decreased significantly (P<.01). Clinical outcome and AVVQ score improved significantly (P<.01) and symptoms had disappeared in 66%. Fifteen of 47 patients with persisting GSV incompetence did not receive additional treatment, because they were asymptomatic.

Independent predictors for success were low C of the CEAP classification, low number of refluxing GSV segments, small diameter of the GSV above the tributary and a positive reflux-elimination test (P<.0001). The reflux-elimination test appeared to be an important independent predictor, with >65% chance of success when positive.

Conclusions: At one year follow-up, treatment with single phlebectomies of a large tributary was effective to abolish GSV reflux in 50% of patients and to free 66% of patients from symptoms. Patients with limited disease progression and mild DUS alterations are most likely to benefit from this approach.

INTRODUCTION

Tributaries represent the major part of the superficial venous system of the lower limbs.[1] From the hemodynamic point of view, they play an important role in patients with varicose veins. Indeed, in the majority of limbs with varicose veins, blood is refluxing as well along tributaries as along a segment of the saphenous veins. Tributaries run parallel or beside the track of an associated saphenous vein but lie outside the saphenous compartment.[2,3] A study on anatomical patterns of the incompetent great saphenous vein (GSV) showed that in 30% of limbs with GSV incompetence above the knee a large incompetent tributary pierces the saphenous fascia at thigh level.[4] Since tributaries are located in the subcutaneous tissue, they are suitable for removal by phlebectomies. Currently there are two main strategies for treating patients having both GSV incompetence and refluxing tributaries. The first strategy consists of GSV treatment (surgical, thermal or chemical) and phlebectomies in a single procedure,[5] while the second strategy consists of GSV treatment only, awaiting tributaries to diminish.[6-12] Both are based on the theory that varicose veins have a descending origin. A different approach would be to treat the tributaries first, thereby sparing the GSV in accordance with the ambulatory selective varices ablation under local anaesthesia (ASVAL) method.[13] If GSV incompetence and symptoms persists, the GSV may be treated in a second stage. It has been shown that phlebectomies improve the hemodynamics of the venous system in the leg and also have a beneficial effect on the segments that have been left untreated.[13-18] The hemodynamic effects of removing refluxing tributaries support the theory of an ascending origin of varicose veins. In a retrospective study with 4 years follow-up, 66% of patients with saphenous and tributary varicose veins were successfully treated by phlebectomy only.[13]

The objective of the present prospective multicenter study was to analyze short-term outcomes after single phlebectomies of a large incompetent tributary joining the GSV at thigh level in patients who also have GSV incompetence. We aim to identify those patients that could benefit from this approach by determining predictors with a prediction model and to verify the value of the reflux-elimination test.

METHODS

Participants

The present trial was designed as a prospective multicenter study at the Departments of Dermatology of the Erasmus MC Rotterdam, Catharina Hospital Eindhoven and Rijnstate Hospital Arnhem. Recruitment of 100 patients started in April 2010; the last patient was included in March 2012.

Consecutive adult patients with symptomatic primary GSV incompetence and a clinically visible incompetent tributary of the GSV at the medial thigh (with or without extension below the knee) were eligible to participate. Incompetence of the GSV and the tributary was defined

as reflux ≥0.5 s at color DUS (Philips, HDI 4500, 10MHz transducer, Andover MA, USA). The tributary had to be clinically visible and/or palpable, making it suitable for phlebectomy.

Exclusion criteria were previous treatment of ipsilateral GSV or tributaries, incompetence of the accessory anterior saphenous vein and tributaries in the thigh, segmental absence of the GSV above the knee, deep venous obstruction, agenesis of the deep venous system, vascular malformations, use of anticoagulant treatment, pregnancy, immobility, significant arterial disease (ankle : brachial pressure index below 0.6) and inability to provide written informed consent to trial participation. The ethical medical committee of the Catharina Hospital Eindhoven approved the study (date 02 March 2010).

Diagnostic methods

Patients were assessed with DUS examination in standing position. The saphenofemoral junction (SFJ), the GSV in the thigh above and below the junction of the tributary, the tributary itself and the GSV below the knee were studied, as well as the small saphenous vein (SSV), the common femoral, femoral and popliteal veins. Valvular function was evaluated in the femoral, popliteal and superficial veins of the thigh by manual calf compression; the Valsalva manoeuvre was performed to assess reflux at the terminal valve of the SFJ. Reflux was defined as retrograde flow >0.5 s. Perforating veins were considered incompetent if >3.5 mm with bidirectional flow.[2,3,19]

For this study, some additional DUS parameters were recorded (Figure 1). Four anatomic GSV segments were distinguished: segment 1 from the SFJ down to the site where the tributary joined the GSV; segment 2 the GSV in the thigh from below the junction of the tributary to the knee; segment 3 was the GSV from knee to mid-calf; segment 4 from mid-calf to ankle. In segment 1 en 2 diameter measurement was performed respectively 2 cm above and below the junction of the refluxing tributary. The total refluxing length of the GSV was recorded. Diameter of the tributary was measured 2 cm below its junction with the GSV. The reflux-elimination test was performed by digital compression of the refluxing tributary in the thigh to test whether this could modify GSV reflux. A slightly modified version of a previously described reflux-elimination test was used, focusing mainly on the effect of finger compression of the tributary on the GSV segment above the tributary's junction.[15] The tributary was compressed at least 5 cm from the junction of the tributary with the GSV, to prevent simultaneous compression of the GSV itself. The reflux-elimination test was considered positive when GSV reflux is eliminated after compression of the tributary.

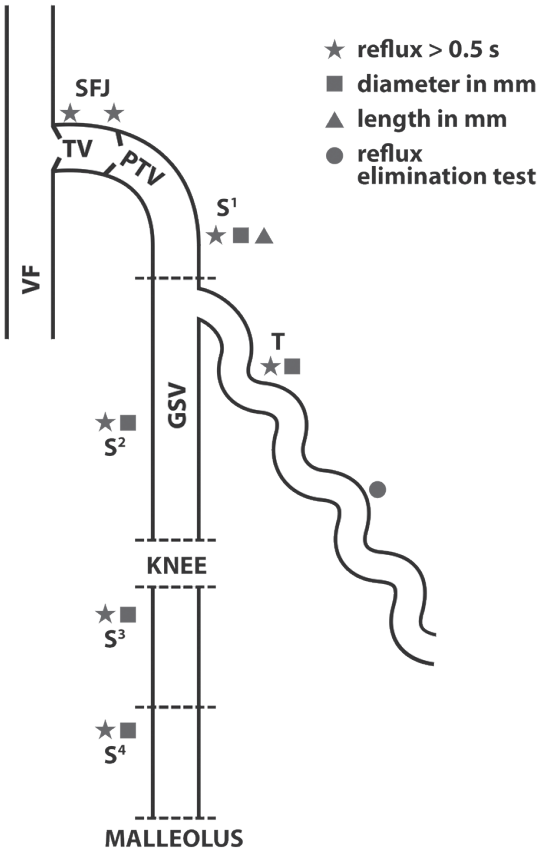
Treatment

Just before phlebectomy, patients were examined with DUS, to verify whether they were validly included. The tributary was marked on the skin with the patient in standing position. Phlebectomy was performed, using local anesthesia with lidocaine 1%. Small phlebectomy

incisions (max. 3 mm) were made and varicose veins were grasped with Oesch phlebectomy hooks, exteriorized, divided and removed.[20]

Medical elastic compression stockings were applied over the wound dressings for the first 48 hours. Patients were instructed to remove the dressings and continue wearing medical elastic compression stockings during daytime for one week. All patients were observed in the clinic for at least half an hour after treatment. Patients were encouraged to mobilize and resume their usual activities as soon as possible.

Figure 1: Baseline duplex ultrasound characteristics of GSV and Tributary.



Abbreviations: SFJ, sapheno-femoral junction; TV, terminal valve; PTV, preterminal valve; VF, vena femoralis; GSV, great saphenous vein; S, segment with reflux; T, Tributary.

Follow-up

Patients were invited for follow-up 3 months after the procedure. C class and VCSS were recorded, patients were asked to complete the AVVQ questionnaire and underwent DUS as described above. If patients presented with persisting symptomatic GSV incompetence, additional treatment was proposed, either by endovenous thermal ablation or ultrasound guided foam sclerotherapy. Patients without GSV incompetence and/or without symptoms were scheduled for a follow-up visit 12 months after the initial procedure. The evaluation at 12 months was identical to the one at 3 months. Patients who had undergone additional treatment were excluded for follow-up, but included in the analysis of total treatment effectiveness; they were assigned as having reflux.

Outcome measurements

Hemodynamic outcome

The primary outcome was absence of reflux in the entire GSV, measured by DUS evaluation after one year. In addition, segmental disappearance of reflux and GSV diameter reduction were studied.

Clinical and patient reported outcome

Secondary outcome measures were C of the CEAP classification,[21] VCSS (range 1-10),[22] and AVVQ score (range 1-100).[23]

Independent predictors for disappearance of reflux

To test for independent predictors of success (defined as no reflux at 12 months) a logistic regression model was used including DUS and clinical measurements.

Reflux-elimination test

A single prediction model analysis was done to evaluate the reflux-elimination test. Because the reflux-elimination test is quick and easy to perform, it would be of great value in clinical practice if it proves to be an important predictor.

Phlebectomy Reflux-Elimination Success Test (PREST) Prediction model

All variables included in the multivariable logistic regression model were eligible for inclusion in the prediction model. Final selection was based on statistical significance after backward deletion. The prediction model is presented as a score chart, from which a total score can be calculated that correlates with a probability of restoring GSV competence.

Statistical analysis

All continuous variables were normally distributed, using the One-Sample Kolmogorov-Smirnov Test. Therefore, data were presented as means with standard deviation (SD); analysis with one sample t-test and paired sample t-test were done to compare groups.

Categorical data were analyzed by means of X^2 test or, if appropriate, Fisher's exact test. This test was also used to evaluate the relation between reflux at the terminal valve and diameter of the GSV and their relation with success. Responsiveness of AVVQ after treatment was tested with paired sample t-test in normally distributed data. The studied patients were analyzed 'per protocol'. To test for independent predictors of restoring GSV competence (defined as no reflux at 12 months) a logistic regression model was used. To avoid overfitting of the prediction model, we calculated the maximum degrees of freedom that could be spend during the regression modelling process with our sample size. This was calculated as *m*/10, where *m* is the limited sample size, which is the smallest group among the outcome. Both success and failure consisted of 47 patients, suggesting that 5 degrees of feedom (df) could be spend. Predictors were initially selected based on literature and clinical expertise (reflux SFJ at terminal valve, number of refluxing segments, C of CEAP, reflux elimination test and GSV diameter above the tributary). Statistically non-significant variables were subsequently removed from the model by backward variable selection based on AIC, corresponding to a P-value of .157 for variables with 1 df. The regression coefficients in the final model were multiplied with a shrinkage factor, which was obtained by bootstrapping (1000 samples). The backward variable selection was taken into account in the bootstrapping. Shrinkage is applied to obtain accurate predictions for new patients; without shrinkage predictions are in general too extreme, resulting in predictions being too high or too low. The final model with the shrunken regression coefficients was presented as a score chart to make the prediction model easy applicable in clinical practice. Calibration (i.e. agreement between predicted and observed risks) was studied. Discrimination (i.e. distinction between successful treatment and treatment failure) was studied using a receiver operating curve (ROC) curve.

A single prediction model analysis was done to evaluate the performance of the reflux-elimination test without any other predictors. We accomplished an internal validation (also obtained with 1000 bootstrap samples).

Statistical analysis was performed using SPSS® version 20.0 (SPSS, Chicago, Illinois, USA) and R 2.15.2 (http://www.R-project.org).

RESULTS

Participants

One hundred eligible patients, with GSV incompetence and an associated incompetent tributary joining the GSV at thigh level, were included. Six patients were lost to follow-up (5 patients did not attend the follow-up visit, 1 patient was treated with EVLA of the GSV

before phlebectomy), and were therefore excluded from the analysis. In total 94 patients were analyzed, 65 women and 29 men. 55.3% patients were classified as C2, 35.1% C3 and 9.6% C4.The mean GSV diameter was 0.55 cm (SD 0.15) above the tributary, and 0.36 cm (SD 0.16) below the tributary. The mean diameter of the tributary was 0.51 cm (SD 0.15) with its junction located at a mean distance of 19.5 cm (SD 6.64) below the SFJ. Half of the patients had terminal valve reflux at the SFJ. In approximately half of the patients reflux was present only in 1 segment. The total refluxing GSV length was <10 cm in 14.9% of the patients, and >30 cm in 29.8% of the patients. Mean VCSS was 4 (SD 1.49, range 2-9) and mean AVVQ score was 10.9 (SD 7.75). (Table I) We found a significant relation between reflux in the terminal valve and diameter of the GSV. In patients without terminal valve reflux, GSV diameter was more often <5 mm and in patients with terminal valve reflux, the diameter of the GSV was often >5 mm. (P<.001). Success was related to a smaller GSV diameter (P=.002) and no reflux at the terminal valve. (P<.001)

Hemodynamic outcomes

In 47 patients (50%) reflux disappeared completely after 12 months. In 15 patients (16.0%) phlebectomy resulted in complete relief of complaints despite persisting GSV reflux after one year of follow-up. Consequently, these patients did not undergo additional treatment. The remaining 32 patients had persisting symptoms and underwent additional GSV ablation. In 57 patients (60.6%) the number of refluxing GSV segments had diminished. However, in 4 patients the number of refluxing segments increased after phlebectomy. The mean diameter of the GSV above the tributary decreased significantly after 3 and 12 months from 0.55 cm to 0.36 cm and 0.39 cm (P<.001) respectively.

Clinical and patient reported outcome

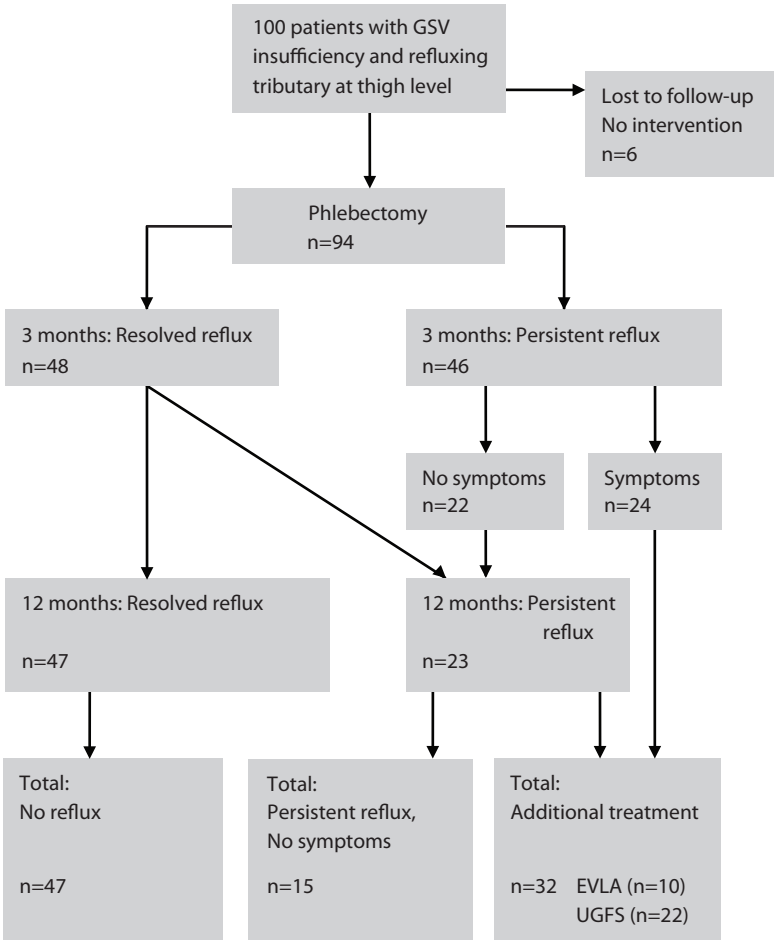
The C of the CEAP-classification decreased significantly after treatment (P<.001); a lower C class was found in 73% of all treated patients. No patient deteriorated. The VCSS and AVVQ scores improved in all patients (independent of hemodynamic effect) after treatment. We found more improvement of VCSS and AVVQ in the patients with hemodynamic success (i.e., no reflux) at 3 months, which remained relatively stable after 1 year (P<.001). The group with persistent reflux showed significantly higher baseline scores and less improvement of HRQoL scores after treatment (Table I). Remarkably, the AVVQ scores improved in 27 patients with persisting GSV reflux. Because of lack of symptoms 15 patients did not undergo additional treatment.

Independent predictors for disappearance of reflux

Reflux was significantly more often abolished when the following parameters at baseline were present: C2 (P<.001); short (<10 cm) refluxing segment (P<.001); reflux in only 1 GSV segment (P<.001); smaller diameters of GSV and tributary (P<.001 and P<.009); a positive

reflux-elimination test (P<.001), and low scores of VCSS (P<.001) and AVVQ (P<.001). Reflux of the terminal valve was seen more often in patients with a diameter >5 mm (P<.001). Success was more often the case in patients with a diameter <5 mm (P=.002).

Figure 2: Flowchart.



Abbreviations: n, number; GSV, great saphenous vein; EVLA, endovenous laser ablation; UGFS, ultrasound guided foam sclerotherapy.

Table I: Demographic, clinical and DUS characteristics at baseline and effectiveness after treatment.

Variable	Total patients	Resolved reflux at month 12 n=47	Persistent reflux at month 12 n=47	P-value
Patient, n=94				
Age, years (range)	53 (21-82)	51 (26-79)	55 (21-82)	.2#
Women, n (%)	65 (69.1)	34 (72.3)	31 (66.0)	.7*
C2, n (%)	52 (55.3)	36 (76.6)	16 (34.0)	
C3 or C4, n (%)	42 (44.7)	11 (23.4)	31 (66.0)	<.001*
AVVQ (SD)	10.95 (7.75)	7.48 (5.44)	14.42 (8.19)	<.001#
VCSS (SD)	4.00 (1.50)	3.38 (1.26)	4.62 (1.47)	<.001#
Duplex characteristics				
Reflux SFJ terminal valve, n(%)	49 (52.1)	20 (42.6)	29 (61.7)	.06*
No reflux terminal valve, n(%)	45 (47.9)	27 (60)	18 (40)	
Refluxing segments				
One refluxing segment (%)	45 (47.9)	35 (74.5)	10 (21.3)	<.001*
More than one segment (%)	49 (52.1)	59 (25.5)	84 (78.7)	
Length of refluxing GSV, n (%)				
<10 cm	14 (14.9)	12 (25.5)	2 (4.3)	<.001*
>10 cm	80 (85.1)	35 (74.5)	45 (97.7)	
Mean diameter GSV above tributary, mm (SD)	5.5 (1.5)	4.9 (1.2)	6.2 (1.4)	<.001#
Mean diameter GSV below tributary, mm (SD)	3.6 (1.6)	3.2 (13)	4.1 (19)	.005#
Mean diameter of tributary, Mm (SD)	5.2 (1.5)	4.8 (1.4)	5.6 (1.4)	.009#
Location of tributary: distance from SFJ, cm (SD)	19.5 (6.6)	18.7 (7.4)	20.2 (5.8)	.3#
Positive reflux-elimination test, n (SD)	61 (64.9)	42 (89.4)	19 (40.4)	<.001*

Abbreviations: N, number; SD, standard deviation; %, percentage; SFJ, saphenofemoral junction; cm, centimetre; GSV, great saphenous vein; mm, millimetre; VCSS, Venous Clinical Severity Score; AVVQ, Aberdeen Varicose Veins Questionnaire
*analyzed with chi-square
analyzed with independent sample T-test

Univariable logistic regression analyses were performed for all variables. After backward deletion of the selected variables, reflux SFJ at terminal valve was removed from the model because of statistical non-significance. In multivariable logistic regression analysis (Table II), C classification and reflux in 1 segment were significantly associated with a successful hemodynamic outcome, independent of all other variables included in the model.

Table II: Univariate and multivariate logistic regression analysis of variables associated with a successful abolishment of GSV competence.

Variable	Univariate model			Multivariate model[a]		
	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age[a]	0.98	0.95-1.01	.2			
Women[a]	1.35	0.56-3.25	.5			
'C'EAP classification[a]						
C2	6.34	2.56-15.68	<.001	4.52	1.50-13.58	.007
C3-4	1			1		
VCSS	0.510	0.36-0.73	<.001			
AVVQ	0.846	0.78-0.92	<.001			
SFJ at terminal valve						
Reflux	1	1				
No reflux	2.18	0.95-4.96	.07			
Refluxing segments[a]						
One refluxing segment	10.792	4.14-28.13	<.001	6.10	1.78-20.87	.004
More than one segment	1			1		
Length of refluxing GSV						
<10 cm	7.71	1.62-36.74	.01			
>10 cm	1					
Diameter GSV above tributary[a]						
<5 mm	3.86	1.57-9.52	.003	2.62	0.80-8.50	.1
>5 mm	1			1		
Diameter GSV below tributary						
<5 mm	4.34	1.43-13.11	.009			
>5 mm	1					
Diameter of tributary[a]						
<5 mm	4.13	1.75-9.77	<.001			
>5 mm	1					
Location of tributary: distance from SFJ						
<20 cm	1.71	0.74-3.91	.2			
>20 cm	1					
Reflux-elimination test[a]						
Positive	12.34	4.14-37.0	<.001	3.42	0.86-13.62	.8
Negative	1			1		

Abbreviations: CI, confidence interval; N, number; OR, odds ratio; SD, standard deviation; %, percentage; SFJ, saphenofemoral junction; cm, centimetre; GSV great saphenous vein; VCSS Venous Clinical Severity Score; AVVQ Aberdeen Varicose Veins Questionnaire

[a] variables selected for the multivariate model based on clinical expertise (MM, TN, MN)

Reflux-elimination test

The result of the reflux-elimination test was significantly different between the group without and the group with persistent reflux. In logistic univariable analysis, a positive test increased the likelihood of having an effective outcome 12 folds (OR=12; 95% CI 4.1-37.0). Despite it the test was no longer a significant predictor in the multivariable model, possibly due to too many variables in a small sample size. A single prediction model analysis for the reflux-elimination test showed that after internal validation (also obtained with 1000 bootstrap samples), patients with a positive test have more than 65% chance of success.

Development of the PREST prediction model

The final prediction model included C of CEAP, number of refluxing segments, GSV diameter (above the tributary) and the reflux-elimination test (Table III). For internal validation, the regression coefficients were shrunken by a factor 0.8316, obtained by 1000 bootstrap samples. The area under the curve of the final model was 0.895. The score chart based on this model is shown in Table III. For example, for patients with GSV reflux in 1 segment (3 points), C2 (3 points), a positive reflux-elimination test (2 points) and a GSV diameter of 5 mm (6 points), the model can predict that phlebectomy will be effective in 90% (total of 14 points).

On the other side a patient with 3 refluxing segments (0 points), C3 (0 points), a negative reflux-elimination test (0) and a GSV diameter of 7 mm (3 points) will not benefit from phlebectomy only (less than 10%, total score 3) and will probably also need GSV treatment.

Table III: Score chart: predicting the probability of resolving reflux of the GSV after treatment with phlebectomy only.

Phlebectomy Reflux-Elimination Success Test (PREST) prediction model									
Number of refluxing segments	1 segment				More than 1 segment				
Points	3				0				
C of CEAP	C2				C3 or C4				
Points	3				0				
Reflux- elimination test	Positive				Negative				
Points	2				0				
Diameter GSV (mm)	<3	3	4	5	6	7	8	9	>9
Points	9	8	7	6	5	3	2	1	0
Total Points	2	6	8	10	11	12	14		
Probability of restoring GSV Competence	0.01	0.10	0.30	0.50	0.70	0.80	0.90		

This scorechart is based on the multivariable model with shrunken beta's using a shrinkage factor of 0.83, which was obtained by 1000 bootstrap samples. Final model with shrunken beta's: Logit (Probability of restoring GSV Competence) = 4.19 – 1.61*Number of refluxing segments – 1.37*C of CEAP + 1.07*Reflux- elimination test – 0.64*Diameter of GSV in mm.

DISCUSSION

Phlebectomy of varicose tributaries is mostly used as treatment in addition to saphenous ablation. However, single phlebectomies affect the hemodynamics of the venous system and can therefore be effective as primary treatment in selective cases. In the present study, we demonstrated that treating only the tributary and sparing the GSV led to complete elimination of GSV reflux in half of the patients. In two thirds of the patients symptoms resolved completely. Also the length of the refluxing GSV segment was reduced and GSV diameter had decreased significantly after treatment of the tributary. An advantage of sparing the GSV is that it can regain its important role as one of the main veins of the superficial venous system. Another advantage of conserving the GSV is that patients can be treated with fewer and less expensive operations, which is safer for the patient and costs less. [13] Moreover, the spared GSV can be used as a natural bypass in case the patient should develop a femoropopliteal deep vein thrombosis of the ipsilateral limb in later life or it can be used for arterial reconstruction (e.g., coronary bypass surgery).

The results of this study support the ascending concept for the origin of varicose veins. The classic descending pathophysiological concept, stating that superficial venous insufficiency starts with valvular incompetence at an escape point (SFJ, saphenopopliteal junction or incompetent perforating vein), and further progresses downwards from the main trunk to the tributaries, is not the sole concept. Contrarily, there is increasing evidence that superficial venous disease has a multifocal origin and can be 'ascending' from the tributaries towards the saphenous trunk, and further to the junction.[1,24-31] Other studies also found evidence for the ascending concept with disappearance of GSV reflux following phlebectomy or ablation of an incompetent tributary,[13,15,24] as well as the reduction in GSV diameter after ablation of a refluxing tributary.[13,15,18,25] In a large retrospective study of patients treated by means of phlebectomies with conservation of the refluxing GSV or SSV, the so-called (ambulatory selective varices ablation under local anesthesia) ASVAL method, reflux in the saphenous veins had disappeared in 69.2% of limbs after one year, and in 66.3 % after 4 years. Diameter at the SFJ had decreased significantly (P<.0001) after 6 months and symptoms were relieved in 84.2% after one year.[13] A prospective study on the effect of isolated phlebectomies on reflux and diameter of the GSV in 54 patients showed significant reduction of reflux and GSV diameter after one month follow-up.[18]

Identification of eligible patients

We found different predictors for hemodynamic success (i.e. abolition of reflux): C2, short refluxing GSV length, only one refluxing segment, small diameter of the GSV and the tributary, positive reflux-elimination test, lower VCSS and lower AVVQ score. A correlation between diameter and reflux of the terminal valve was seen as described before.[32] Length of GSV reflux was also found to be a predictor in a previous study. Several studies showed that the presence

of reflux below the knee and especially down to the malleolus before treatment was much more frequent in the group of limbs with persisting reflux after phlebectomies.[1,13,18,26,27]

These findings show that this therapeutic strategy works best in patients with mild disease and limited DUS changes.

Patients with mild venous disease may benefit from the strategy to remove the tributary first. If treating the tributary fails to abolish the reflux of the GSV it might be due to progressed venous disease (i.e. larger GSV diameter, longer refluxing segment or higher C) or to a descending cause of GSV insufficiency (insufficiency at the SFJ.

Reflux-elimination test

This test showed a strongly significant positive correlation in patients with hemodynamic success. When the test is positive, the chance of treatment success is >65%. The outcome was independent of the C of CEAP, extent of reflux, diameter of GSV or tributary. The reflux-elimination test is thus an independent and strong predictor for treatment success. Because it is a quick test and very easy to perform, its introduction in daily practice is feasible. It can be a valuable addition to the CEAP classification, GSV diameter, extent of reflux and VCSS and AVVQ scores, which are also good predictors for success.

The prevalence and severity of superficial venous insufficiency increases with age[33,34] and, the number of patients with varicose veins will expand. Studies have shown that treatment of varicose veins is not only cost-effective,[35] but also improves patients' quality of life.[36] Patients' reported outcome is an important parameter for treatment choice, and it can be used to prevent overtreatment. In the present study AVVQ score improved in all patients after treatment. Pittaluga et al.[18] also showed that symptoms improved in all patients after phlebectomy, regardless of abolition of saphenous reflux. Probably, phlebectomies reduce the total refluxing volume, explaining the clinical and hemodynamic improvements, even if saphenous reflux persists.[18] Obviously, we should not only focus on saphenous reflux, which is a surrogate outcome parameter, but also take into account patients' symptoms. The ultimate goal of any venous treatment should be to improve patients' quality of life and to prevent complications, not to improve duplex determined anatomic and hemodynamic findings.[37-39] The presence of reflux does not necessarily correlate with functional impairment or clinical disease.[16,36]

The present study clearly illustrates that treatment of varicose vein patients should be individualized. Instead of a 'one size fits all' strategy, a well-considered 'à la carte treatment' should be preferred. Indeed, every patient is different, not only considering anatomy and hemodynamics, but also the clinical presentation and the impact of varicose veins on the patient's quality of life and symptoms. In modern phlebologic practice, quality of life, symptoms, clinical signs and DUS findings should be carefully assessed to decide on the best treatment strategy for each individual patien.[38] The predictors for success found in the

present study may orient the physician toward a less invasive approach, which may consist of single phlebectomies in properly selected patients. Even in the presence of saphenous reflux, phlebectomies may be the first-line treatment avoiding needless saphenous ablation. Also, multiple treatment sessions can be avoided by selecting the patients who have an advanced stage of disease; they can be treated with a combination of GSV ablation and phlebectomy in one session.

Limitations

A possible limitation is the lack of external validation of the prediction model. A new larger group of patients should be studied to test the validity and reliability of this model. Not all variables could be included in the prediction-model due to the sample size. A second limitation is the short follow-up of only one year. This follow-up period was chosen because we wanted to evaluate short-term effectiveness of single phlebectomies and we wanted to determine predictors for success. Long-term follow-up is needed to assess whether the favorable hemodynamic outcomes are durable over time.

A third limitation of this study is that the majority of patients had C2-C3 disease. The effectiveness of single phlebectomies as a primary treatment may be less in patients with extended venous disease (C4-6).

Conclusion

At one year follow-up, treatment with single phlebectomies of a large tributary was effective to abolish GSV reflux in 50% of patients and to free 66% of patients from symptoms. Patients with less extended disease benefit from this approach. Predictors for success are C2, reflux in only one segment (<10 cm), small diameter of the GSV (<5 mm), and a positive reflux-elimination test. By using these predictors and the PREST prediction score chart, physicians can evaluate the probability of success after single phlebectomy for each individual patient.

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Chapter 6

New Concepts on Recurrence of Varicose Veins According to the Different Treatment Techniques

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ABSTRACT

Recurrent varicose veins remain a common problem after varicose vein treatment. Several etiologies have been recognized: tactical and technical failure, neovascularisation, recanalisation of a previously obliterated trunk and progression of the disease. With the widespread use of duplex ultrasound and increasing experience in the field of ultrasound-guided procedures, the impact of both *tactical and technical failure* is likely to diminish. However this issue still needs our attention, as it may induce early recurrence after all types of intervention. Another etiologic factor is *neovascularisation*, occurring in particular after surgery at the level of the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ).

To explain recurrence after endovenous ablation (EVA) the focus has rather been on *recanalisation* of a previously obliterated trunk. It is well known that such recanalisation occurs more frequently after chemical ablation with sclerosant foam than after thermal ablation. The incidence of neovascularisation at the SFJ or SPJ is much lower after EVA than after surgical procedures. However this does not mean that the junctions are never involved in recurrence after EVA. It is therefore also important to follow the evolution at the level of the SFJ or SPJ by means of duplex ultrasound, as new (or persistent) reflux may be detected sonographically.

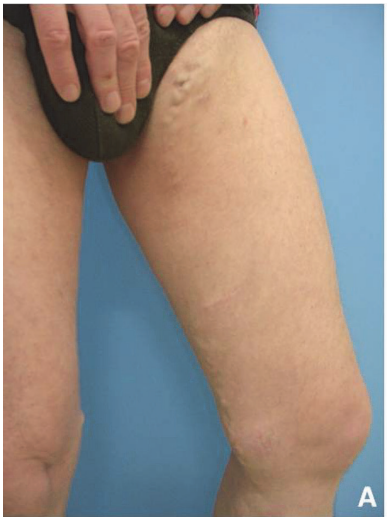
Progression of the disease cannot be avoided and is an important contributory factor in the pathophysiology of recurrence at long term. Apart from genetic factors, other patient-related factors (e.a. BMI ≥30, pregnancy after the intervention) have been claimed to be responsible for progression of the disease and hence recurrence. Due to disease progression after several years, tortuous neovascular veins or (newly) refluxing veins at the junction may connect with superficial varicose veins of the thigh or leg, acting as a 'joint venture' and in this way lead to the clinical situation of a full-blown recurrence of varicose veins.

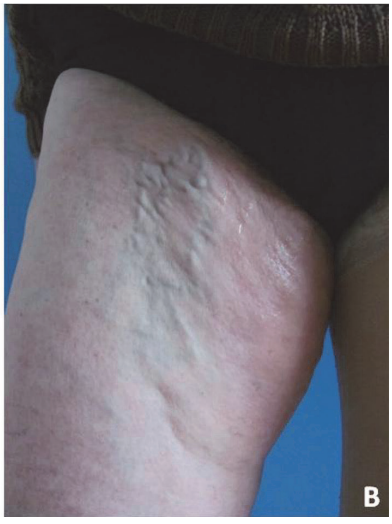
To increase our understanding of varicose vein recurrence, future studies are needed, including adequate preoperative duplex ultrasound investigation and long-term follow-up with serial duplex scans, after different forms of varicose vein treatment.

Introduction

Recurrent varicose veins remain a common problem. It has been extensively studied after surgical treatment of varicose veins, but is now also increasingly encountered in patients treated with endovenous techniques (Figure 1A and B). After surgery the incidence of clinical recurrence after 5 years is estimated to be between 25 and 50% according to prospective studies.[1,2] After endovenous thermal ablation (EVTA) the 5 years incidence of recurrence is less well documented so far, as studies with long term follow-up are still scarce. After treatment of the great saphenous vein (GSV) with radiofrequency, using the Closure Plus® system, Merchant et al[3] reported an incidence of 27% of varicose vein recurrence after 5 yrs. According to the 3-year results after treatment with radiofrequency powered segmental ablation (Closure Fast®), the incidence of recurrent varicose veins was 33%.[4] Five years after endovenous laser ablation, recurrent varicose veins were present in 31% of limbs treated without SFJ ligation and in 49 % of those treated with additional high ligation.[5] Finally, although occlusion rates seem to be inferior after ultrasound guided foam sclerotherapy (UGFS), clinical results are very comparable to those of surgery and EVTA, at least at short- and mid-term follow-up, according to recently published randomised controlled trials.[6,7] Five year results of these ongoing trials, including those after UGFS, are still awaited. In summary, the available data illustrate that clinical reappearance of varicose veins definitely remains a problem after whatever technique used for primary treatment of patients suffering from varicose veins (C2) with or without chronic venous insufficiency (C3-C6).

Figure 1 A and B: Similar clinical appearance of recurrence 5 years after surgery (A) and 5 years after endovenous laser ablation (**B**).





ETIOLOGY OF VARICOSE VEIN RECURRENCE

Although duplex ultrasound has been introduced in phlebological practice all over the world, there may still be a problem of insufficient understanding of venous anatomy and haemodynamics, which may indeed be very complex in certain cases. This may lead to *tactical failure.* On the other hand, incorrect or insufficient surgical or endovenous intervention may lead to *technical failure*. Both tactical and technical failures are obvious causes of recurrence of varicose veins after treatment.

Neovascularisation has been extensively studied as another cause for developing recurrence. This term describes new, usually tortuous, venous channels at the site of a previous (high) ligation e.g. between the saphenous stump on the common femoral vein (CFV) and a residual GSV, anterior accessory saphenous vein (AASV), posterior accessory saphenous vein, Giacomini vein or superficial thigh tributaries.[8] It is easily detectable by means of duplex ultrasound after an intervention for varicose veins.[9] It has mainly been studied at the saphenofemoral junction (SFJ) after GSV treatment. However it may equally be seen at the saphenopopliteal junction (SPJ) after small saphenous vein (SSV) surgery (Figure 2), as well as after ligation of incompetent perforating veins, or even after phlebectomies. The term neovascularisation has now been recognized as one of the Vein Terms, and has been defined as: 'presence of multiple small tortuous veins in anatomic proximity to a previous intervention'.[10] A more purely sonographic descriptive term may be used for the typical appearance of these veins at duplex ultrasound, namely 'groin varicose network' at the SFJ or 'popliteal fossa varicose network' at the SPJ.[9] Neovascularisation can also be observed after surgery in the strip track. It appears as a single usually very tortuous refluxing vessel in the saphenous compartment (Figure 3). In such case, the source of reflux is usually a persisting incompetent junction, an incompetent perforating vein, or incompetent tributaries draining into the tortuous vein.

Recanalisation of the ablated trunk (after initial obliteration) is a specific concern after endovenous thermal or chemical ablation. Duplex ultrasound then reveals partial or complete reopening of the trunk, with or without reflux (Figure 4).[9] There may be a connection with a persisting incompetence of the SFJ terminal valve or of the SPJ, an incompetent perforating vein, or tributaries with or without reflux.

Finally, the most important cause of recurrence is *progression of the disease*. One should never forget that superficial venous disease is a chronic condition, which tends to progress over time. This means that after an intervention, other previously unaffected superficial veins or perforating veins may become incompetent and truncal reflux may extend to a previously competent segment. In some cases abdomino-pelvic venous insufficiency may also play a role in progression of the disease.[11] Other underlying genetic and constitutional risk factors for disease progression are poorly understood up until now. It is generally accepted that there is a strong family predisposition, not only for having varicose veins but also for developing recurrence. The exact nature of the genetic basis for this family predisposition, however, is far from clear. To shed more light on this issue, it will not be sufficient to study single genes,

potentially implicated in venous disease. Instead, genome wide association studies will be needed using very large sample sizes, to further unravel the genetic basis of chronic venous disorders.[12] Several constitutional risk factors, which could possibly enhance the tendency for developing varicose vein recurrence, have been recognized, such as female gender, left sided disease, obesity, multiple pregnancies and subsequent pregnancies after initial treatment, severe chronic venous disease (C4-C6 of the CEAP classification), and associated deep vein incompetence.[13]

Figure 2: Duplex ultrasound of the popliteal fossa. Longitudinal image. Neovascularisation at the SPJ after small saphenous vein surgery.

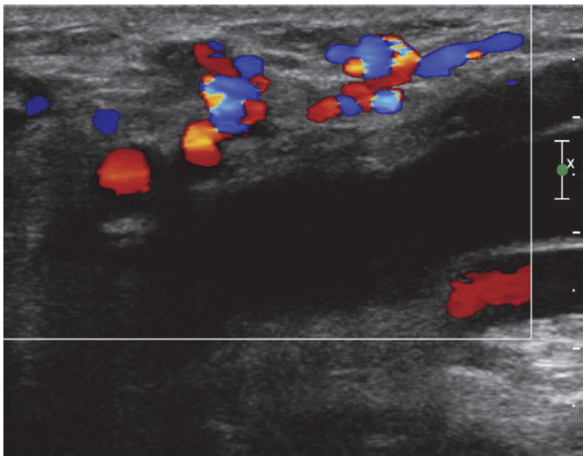


Figure 3: Duplex ultrasound of the posterior calf (longitudinal image). Neovascularisation in the strip track of the SSV, 7 years after stripping.

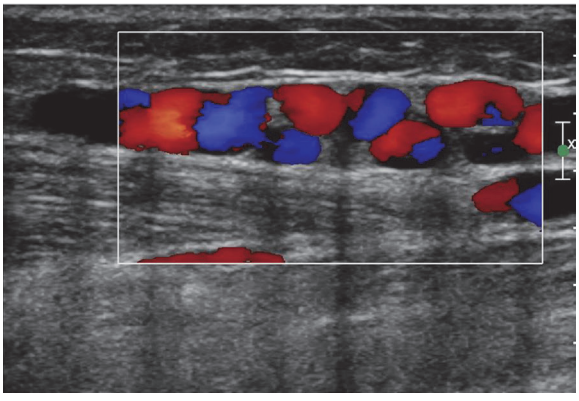
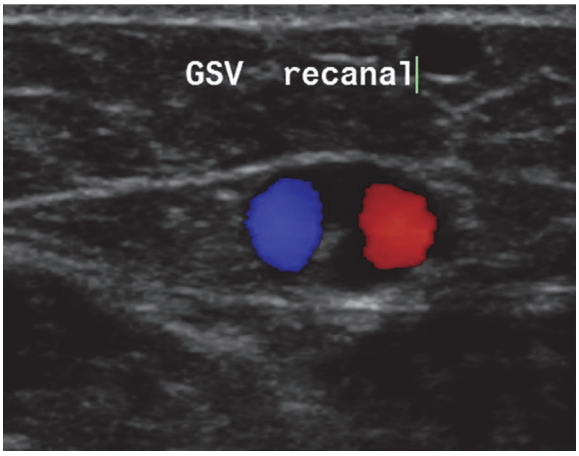


Figure 4: Duplex ultrasound of the GSV 10 cm under the SFJ (transverse image). Recanalisation with 2 tortuous channels 3 years after endovenous laser ablation.



PATHOPHYSIOLOGIC MECHANISMS

Tactical and technical failure

The pathophysiology of varicose vein recurrence due to tactical and technical failure is rather obvious. If treatment has been incorrect or incomplete, incompetence may persist which may lead to early clinical recurrence. If incompetence persists at the SFJ, the 'pathway' of reflux may typically run through the residual AASV, from the SFJ to mid thigh, and then further down, presenting as recurrent varicosities on the anterior thigh and leg. This case can occur after surgery but more typically after endovenous ablation. If only the refluxing GSV has been ablated, and a large refluxing AASV has been left untreated, reflux can persist in the incompetent SFJ and AASV. This may occur even after correct position of the tip of the thermal ablation device during the initial procedure, as the AASV usually joins the SFJ only cranially from the highest point of ablation. Therefore, if both GSV and AASV are large and refluxing, it is wise to ablate both at once.

Neovascularisation

After a classic surgical intervention for varicose veins, the role of neovascularisation at the junction has been extensively investigated. It has been reported to account for 8 to 60% of varicose vein recurrences.[2,8,14-17] Contrarily, after EVTA, neovascularisation at the SFJ or SPJ is a very exceptional finding, with an incidence between 0-1% and this process does not seem to play an important role in recurrence.[5,18] After surgery including high ligation, various pathophysiologic mechanisms may be involved inducing neovascularisation: angiogenic stimulation in the stump endothelium, transnodal lymphovenous connections, dilatation of small adventitial vessels, vasa vasorum of the femoral vein, and disturbed venous drainage of

the ligated tributaries of the SFJ.[8,19-22] After EVTA, physiologic drainage of abdominal and pelvic tributaries is maintained, as ablation only is started distally from the ostium of the superficial epigastric vein. It is also possible to mimick this situation by performing a surgical intervention, consisting of ligation of the SFJ distally from the orifice of the superficial epigastric vein, instead of a 'flush' ligation at the very junction. Pittaluga et al.[23] reported a very low rate of neovascularisation (1.8%) two years postoperatively after this kind of procedure. Future prospective studies will be needed to further elucidate this pathophysiologic issue.

Recanalisation

After endovenous thermal or chemical ablation, recurrence is mainly due to recanalisation of the ablated trunk. Several factors may influence the rate of recanalization, such as the vein diameter and the amount of energy delivered to the vein wall. Larger veins, treated with UGFS, tend to recanalise more easily than smaller veins.[24] After thermal ablation recanalisation may occur more easily if the vein has been treated with insufficient energy.[25] After EVTA, it has also been suggested that vasa vasorum could play a role in the recanalisation process. Labropoulos et al.[26] described tiny arterial vessels entering the vein and postulated these could be responsible for recanalisation and recurrence. As this issue is far from clear, it would be worthwhile to investigate this further by means of detailed duplex ultrasound studies after different types of ablation procedures.

Progression of the disease

The above described underlying pathophysiologic mechanisms probably interact with progression of the disease to cause early or late recurrent varicose veins in an individual patient. In some patients early recurrence may appear within the first year after a previous intervention, whereas it may take several years for recurrent varicose veins to develop in other patients. Probably there is always a 'joint venture' between phenomena occurring at the junction and the presence of superficial refluxing veins in the thigh or leg (Figure 5). It is not yet clearly understood why these (new) refluxing superficial veins tend to reconnect over time with those at the junction. Probably there are some chemotactic signs involved in this reconnection process in addition to other, still to be unraveled, mechanisms. Such a 'joint venture' can be observed after initial surgical treatment as well as after endovenous ablation:

Recurrence after surgical treatment

After high ligation and stripping of the GSV, recurrence can appear in the *early* postoperative stage if residual varicose veins or a refluxing GSV, anterior or posterior accessory saphenous vein, or Giacomini vein, persist. Prompt reconnection between the latter pathologic veins and neovascular veins can be quite evident in such situation.[16] Recurrence developing *late* after surgery is more often primarily due to progression of the disease with neovascularisation playing only a secondary role in these cases. After a few years new varicose veins develop

in the leg and these can connect with initially tiny neovascular veins in the groin, which at the long term can become larger and refluxing. This leads to the typical clinical presentation of thigh or whole leg varicose vein recurrence several years after surgery (Figure 6). In other cases, one or more perforating veins (e.g. at mid thigh) are acting as a source of reflux, due to progression of the disease.

Figure 5: Joint venture between phenomena at the SFJ or SPJ and truncal or superficial veins in the periphery may lead to clinically relevant varicose vein recurrence.

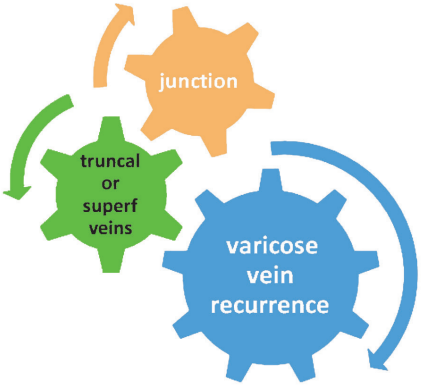
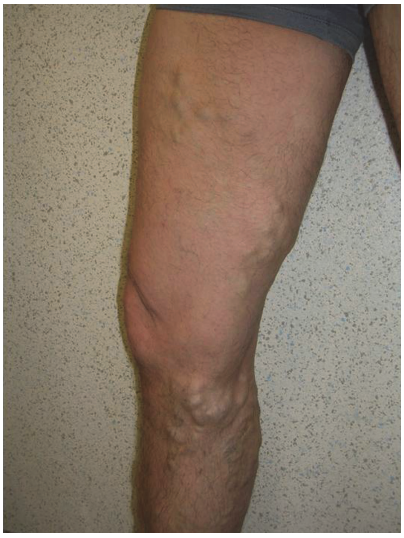


Figure 6: Patient operated on 12 years earlier (high ligation and stripping of the GSV with phlebectomies) by one of the authors (MDM). Recurrent varicose veins due to neovascularisation at the SFJ reconnecting with the AASV and extensive varicose tributaries.



At the level of the SPJ pathophysiology of recurrent reflux has not been studied that extensively. If surgery has been limited to flush ligation at the SPJ – a common practice in certain countries like e.g. the Netherlands – large tortuous neovascular vessels can reconnect the SSV stump with the refluxing SSV trunk. In such case, the refluxing SSV can be easily treated by means of EVTA or UGFS. After initial stripping of the SSV to mid-calf level, neovascularisation at the SPJ may result in formation of new tortuous veins running from the popliteal fossa downwards, either in the saphenous compartment of the SSV (Figure 2) or as superficial veins in the calf. Another particular feature in the popliteal fossa is the presence of a popliteal fossa perforating vein, which is easily recognised in front of the lateral condyle of the femur and gives rise to typical tortuous veins running from the lateral popliteal fossa towards the calf.[9] This vein usually has no connection with the SSV and therefore such varicose veins may rather be related to progression of the disease after any previous treatment.

Recurrence after endovenous treatment

Similar to what can be observed after surgery, there can be interaction between recurrent or persisting reflux at the junction and superficial refluxing veins after endovenous ablation as well. Unfortunately, in the majority of studies looking at outcome after EVTA of the GSV the fate of the SFJ is not even mentioned. Only a few randomised trials, which compare EVTA with surgery, have investigated the incidence of new reflux at the SFJ. In the recently published German RELACS-study,[27] duplex-detected reflux at the SFJ appeared to occur significantly more frequently after endovenous laser ablation (17.8%) than after high ligation and stripping (1.3%). It should be mentioned that in the surgical group a particular technique had been used to mitigate the effect of neovascularisation at the SFJ, by invaginating the GSV stump with a non-absorbable suture. This might explain somehow why the incidence of postoperative recurrent reflux at the SFJ was so low. Moreover, all procedures were performed under local tumescent anesthesia, which facilitates dissection at the SFJ and minimizes blood loss. It may be hypothesized that both these factors reduced surgical trauma and haematoma formation, and hence the incidence of neovascularisation.[19,27]

In the recent UIP Consensus Document on duplex evaluation after treatment the importance of reporting the findings at the SFJ or SPJ after all types of treatment has been extensively discussed.[9] After endovenous thermal or chemical ablation, persistence or re-appearance of reflux at the SFJ or SPJ and/or at the level of the saphenous stump is always to be considered pathological. In such case, serial duplex ultrasound examinations can demonstrate reconnection between the incompetent most cranial part of the GSV in the groin and recurrent thigh varicosities, even if the main trunk remains obliterated. In case of partial or complete recanalisation of the GSV after ablation, reflux may of course be transmitted from the SFJ directly to the recanalised GSV trunk. The same may occur at the level of the SPJ and SSV. To further clarify this issue, more studies looking at the fate of the SFJ or SPJ after different treatment forms are to be awaited.

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Chapter 7

General Discussion

TREATMENT OF 'CHOICE'

The standard of care for treating insufficient saphenous veins has been ligation plus stripping for more than 100 years. In the last decade, the introduction of minimally invasive (endovenous) techniques has changed the approach of primary saphenous insufficiency. Endovenous thermal ablation (EVTA) techniques, always performed under duplex ultrasound (DUS) guidance, appeared to be very effective treatments with high success rates at short-term follow-up and an excellent side-effect profile. For these reasons, EVTA treatments were implemented almost immediately after their introduction in several countries including the Netherlands. Recently, the Dutch guideline for treatments of venous disease has been updated; the new guideline recommends EVTA as the first treatment choice for saphenous insufficiency.[1] The Dutch patients association for vascular diseases ('Hart & Vaatgroep') has formulated quality criteria ('spatader keurmerk') for performing varicose vein treatments. One of the requirements for a varicose vein clinic to receive a quality mark is that it performs more than 95% of the treatments of primary saphenous insufficiency endovenously. These recent changes indicate that EVTA treatments have expelled classic surgery shortly after their introduction.

Reimbursement of varicose veins treatments is controversial in many western countries. The Dutch Health Care Insurance Board (CVZ) has recently restricted reimbursement of varicose vein treatments. The Board decided to restitute treatment costs only for those patients that are classified C3 and higher according to the CEAP classification. There are at least three reasons to object to this decision. First, the CEAP classification is not a classification for varicose veins alone but for venous disease. The C2 category is the only C that describes varicose veins; all the other C categories do not comprise the presence of varicose veins. Basing the decision of varicose vein treatment on the category of CEAP seems therefore very illogical. Secondly, varicose veins are very likely to progress into advanced stages of venous disease; 30% of patients with C2 progress to C3 and 10% from C3 to C4 (unpublished data from the Bonn Vein Study).[2] Therefore, treatment of varicose veins may prevent progression of venous disease and eventually be cost-effective. Although there are several indications that venous disease will progress, scientific evidence of the natural course of venous disease is scarce.[3,4] This lack of evidence is the direct result of the character of venous disease. It is impossible to randomize patients into two groups (treatment versus no treatment), because patients who have symptoms will have the wish to get treatment for their varicose veins.[5] Longitudinal observational population based cohorts such as the Bonn Vein Study may help to answer these questions.[6,7] The third reason is that the appearance of varicose veins, the presence of edema or the results of DUS examination are not a good predictor of patient reported outcomes (PROs).[8,9] Therefore, PROs should also be incorporated in assessing the varicose patient and deciding about treatment.

Another important reimbursement issue in the Netherlands concerns ultrasound guided foam sclerotherapy (UGFS). Due to the lack of evidence UGFS reimbursement has been debated.

Because UGFS has lower occlusion rates in primary saphenous veins than EVTA treatments, it is reimbursed as such. It can however be reimbursed as standard sclero-compression therapy which does not include the use of DUS. UGFS is very valuable in specific cases. Sometimes it is the best and only option, for example in patients with tortuous veins, neovascularization after stripping and in patients with contraindications for more invasive treatments.[10] UGFS is easy to perform, cheap and well tolerated by patients and it results in the same improvement in patients reported outcomes as EVLA and conventional stripping.[11,12]

In addition to reimbursement criteria, there is the issue of treatment indication. Not all patients are in medical need of treating their varicose veins. In some patients the likelihood of having symptom reduction after treatment is low. Lower leg symptoms are fairly non-specific and symptoms such as restless legs may persist even after successful treatment.[12] Other patients primarily seek cosmetic benefit and this should be clearly recognized and acknowledged.

Most importantly, throughout the process of treatment indication, physicians should take into account the extent of symptoms, venous disease severity and its complications, patient preferences, impact of the disease on patients' life (i.e. HRQoL), the likelihood of HRQoL deterioration due to disease progression, and treatment related adverse events and costs. Particularly in view of growing expenses for healthcare and limited financial resources proper patient selection is useful to avoid unnecessary treatments.

ASCENDING THEORY

The principles of venous hemodynamics are much more complex than previously thought. The classic descending pathophysiological concept is no longer accepted as the only 'truth'. The descending theory signifies that superficial venous insufficiency starts with valvular incompetence at an escape point (i.e., saphenofemoral junction, saphenopopliteal junction, or perforating vein) and further progresses downwards from the main trunk(s) to the tributaries. There is now growing evidence that in many cases superficial venous disease is multifocal and rather 'ascending' from the tributaries towards the main trunks and further to the junctions.[3,4,13-16] Both ascending and descending etiology most likely exist. The surgical approach focusing on the treatment of the 'varicose reservoir' (i.e. tributaries) by means of phlebectomies with conservation of a refluxing saphenous trunk is enjoying renewed attention. Treating insufficient tributaries of the insufficient saphenous vein may lead to abolition of the saphenous reflux in the trunk, saving the saphenous vein.[17] This re-lived concept challenges the commonly practiced approach to treatment of venous insufficiency, which usually focuses on the treatment of the refluxing saphenous trunk. The results of our study imply that by treating tributaries first, the hemodynamics may improve (Chapter 5), but this should be better studied in clinical RCT studies. The treatment of tributaries by phlebectomies and UGFS has been practiced for many years. Our study has contributed to the evidence for the ascending theory; we found that great saphenous vein (GSV) reflux disappears in 50% of the patients

after phlebectomy of the tributary and in 66% of the patients also symptoms disappear. This approach seems to be effective in a selective group with less extended venous disease (i.e. C2, short refluxing segment of the GSV and a diameter less than 5mm). In patients presenting with extensive varicose veins and a clearly dilated refluxing saphenous trunk from SFJ to the medial malleolus, it might be wiser to treat the refluxing trunk with concomitant phlebectomies of large tributaries in direct connection with the saphenous vein in a first stage.[18] If treating the tributaries fails to abolish the reflux of the GSV, it might be due to progressed venous disease or to a descending origin of the insufficiency (i.e. terminal valve reflux).

OUTCOME MEASURES OF VARICOSE VEIN TREATMENT

Complete obliteration and reflux, measured by DUS examination are often the primary and most important end-points in studies concerning varicose vein treatment. PROs are considered a secondary outcome. Only a few studies address the importance of HRQoL as effectiveness measurement for patients with varicose veins.[12,18,19] Reflux is generally used as objective parameter to measure incompetence of veins. When reflux has disappeared after treatment, the treatment is considered effective. However, there are patients without venous reflux who have significant venous symptoms. The opposite also exists, some patients with venous reflux have no symptoms at all (i.e. patients in a compensatory phase). The outcomes of the MAGNA trial (Chapter 4) illustrate that having reflux does not necessarily result in symptoms.[11] We found that 14% of the patients treated with UGFS did not receive an additional treatment because their symptoms had disappeared after treatment. The primary outcome measure of our MAGNA trial was absence of reflux; consequently the UGFS patients with persistent reflux were considered treatment failures. In fact, these patients could also be considered as treated successfully, because their symptoms had disappeared and their HRQoL scores had improved as much as the ones without reflux. The effectiveness of UGFS for primary saphenous veins is considered to be lower than of that of EVTA treatments and surgery, but this efficacy is based on DUS based parameters. Based on PROs however, UGFS could be considered as effective as the other treatment options. Five year results need to confirm the persistence of improved PROs in time.

Our second clinical trial (Chapter 5) also proved that reflux may not be the only valuable treatment outcome. In this trial, 16% of the patients did not need an additional treatment since they lacked symptoms despite their remaining GSV reflux.[18] Phlebectomy of tributaries resulted in reduction of refluxing segments and diameter of the GSV and improvement of PROs. These results suggest a relation between the extent of the venous reservoir and the symptoms of the patient. In case the venous reservoir has been diminished after treatment, also symptoms may disappear independent from persisting reflux.

The results of our studies show that we should not only focus on saphenous reflux as treatment outcome but take into account patients' symptoms as well. The ultimate goal of any venous

treatment should be to improve patients' quality of life and to prevent complications, not to improve findings on anatomic and hemodynamic assessments.[8] The presence of reflux does not necessarily correlate with functional impairment or clinical disease.[20,21] These paradoxical observations confirm that there is a need to clearly identify patients that are most likely to benefit from venous therapy. Instead of a simple approach (C3 and more) a prediction model including patient and disease characteristics (symptoms, extension of disease on DUS, disease severity, and complications) may assist in optimal patient selection.

À LA CARTE TREATMENT

Treatment à la carte means individualized treatment, a treatment strategy based on the specific characteristics of a patient. Every patient is different, not only anatomically and hemodynamically, but also in his symptoms and in the impact on quality of life that his varicose veins induce. For deciding about the best treatment strategy for the individual patient, quality of life, symptoms and DUS investigation should be assessed and evaluated.

We advocate that we should not only treat the varicose reflux, but we have to offer patients an 'à la carte' treatment that is based on assessing the individual patient in multiple perspectives. For example, an immobile patient with a small refluxing GSV that is associated with considerable symptoms will have a greater risk to develop venous complications than a young healthy person with similar GSV reflux. One could decide to treat the GSV of the first patient and be conservative with the latter patient. To assist in an individualized treatment plan, the extent of symptoms should be assessed with disease specific PRO instruments.

The superficial venous anatomy is far more complex than what is represented in the classic anatomical textbooks. Our understanding of the superficial venous anatomy and hemodynamics has improved considerably during the past 20 years thanks to the introduction of DUS investigation.[22] DUS has led to a refinement in the description of lower limb venous anatomy, in particular by distinguishing between the main saphenous trunks, within the fascial compartments, and the tributaries, situated subcutaneously, outside the saphenous compartment.[23] Modern varicose vein treatment is completely based on this 'duplex anatomy' and its particular hemodynamics, which may be very different from one patient to the other, and even may differ between the right and the left leg in an individual patient. This explains why a 'one size fits all' approach is not applicable for patients with varicose veins.

In view of the rapid evolution of available equipment and treatment possibilities for varicose veins, a more rational approach is mandatory. It is therefore important to identify objective criteria for choosing an à la carte treatment for each individual patient. Examples of such criteria could be patient-related, such as a low HRQoL score, and/or based on anatomic and hemodynamic parameters such as a minimal diameter of the varicose vein.[19] Such criteria will not only allow selecting the most efficient treatment technique(s), but will also help to exclude inappropriate treatment options.

FUTURE

We now have some large well-designed RCTs from different countries showing that the minimal invasive interventions are preferable to surgical therapy. However these results need to be confirmed on the long term.

Having several very successful interventions for primary saphenous varicose veins, the future challenge is to select the patients that are most likely to benefit from these therapies and to choose the most appropriate therapy for each individual patient. By doing so, we will avoid unnecessary therapies, reduce costs and provide the best possible care for our patients. In an era of health technology assessment and cost-effectiveness analysis, treatment related costs will become increasingly important and this will certainly remain an important issue in the future. First of all, it is important to identify those patients who are in medical need for therapy. To be able to select these patients, more evidence of varicose disease progression is needed. Secondly, consensus criteria should be formulated to assist in management decisions for individual patients with varicose veins. With the adaptation of minimally invasive procedures and the choice of techniques on a case-by-case basis and with the abandonment of needlessly destructive treatments we can improve varicose veins treatment strategies.

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Chapter 8

Summary / Samenvatting

SUMMARY

Chapter 1 is a general introduction of this thesis. Venous insufficiency of the lower extremity is common and the prevalence increases with age. Chronic venous disease (CVD) has a high impact on patients' health related quality of life (HRQoL) and is associated with considerable health care costs. Varicose veins are part of CVD and are very common. Since more than hundred years, surgical ligation of the junction with or without stripping has been the standard of care in the treatment of insufficient great and small saphenous veins. In the last decade several minimally invasive techniques have been introduced to improve efficacy, patients' HRQoL and treatment satisfaction, and to reduce serious side effects, costs and postoperative pain. This chapter ends with the motivation and aims of this thesis.

Chapter 2 gives an overview of the different minimally invasive treatment options. Classic surgery has a relatively high recurrence rate and not an optimal side-effect profile. Since more than 10 years minimally invasive treatments are available and they challenge surgery as the standard of care in patients with saphenous varicose veins. Ultrasound guided foam sclerotherapy (UGFS), endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are the most commonly used endovenous therapies. With a review we inform clinicians about the therapeutic options for insufficient saphenous varicose veins and describe and compare the indications, procedures, efficacy and safety profile of each endovenous treatment.

Chapter 3 discusses different instruments that can be used for assessing patient reported outcomes, both generic and disease-specific instruments. Not surprisingly, patients suffering from CVD may have substantial HRQoL impairment because of the appearance of varicose veins, the symptoms and complications of varicose veins and CVD. Several studies confirmed that treatment of venous disease improved HRQoL. In addition to generic HRQoL instruments, such as the Short Form (36) Health Survey (SF-36) and the EQ-5D, which have been used in patients with CVD, disease-specific instruments provide more information about the impact of CVD and varicose veins on patients' daily lives. The three most commonly used disease-specific HRQoL tools for varicose veins and CVD are the Aberdeen Varicose Vein Questionnaire (AVVQ), the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) and the VEINES Sym/Qol. These questionnaires are all designed to provide specific information and can be used for different study aims. Until now only the AVVQ was translated and validated for the Dutch language.

In this chapter we describe the translation and validation of the CIVIQ and the VEINES Sym/Qol in two separate studies for Dutch patients with varicose veins. Several psychometric properties were tested in heterogeneous groups of Dutch patients treated for varicose veins. We concluded that both validated questionnaires are feasible and reliable for use and that the CIVIQ also has a good responsiveness.

In chapter 4 we describe the results of the randomized controlled *MAGNA-trial*. This RCT compared the anatomical success rate, frequency of complications, and HRQoL improvement of EVLA, UGFS, and conventional surgery (CS) for the treatment of primary great saphenous vein incompetence. The study showed that the 1-year efficacy, defined as anatomical success based on duplex ultrasound examination, was equally high for EVLA and CS and lower for UGFS. All the treatments were safe, no serious complications were seen. Wound infections and neovascularisation were more common after CS. All therapies resulted in significant clinical and HRQoL improvement. Long-term efficacy of these three treatments will be available in 2015.

Chapter 5 describes the results of a prospective study, which evaluates the effect of phlebectomy on great saphenous vein (GSV) insufficiency. Phlebectomy of varicose tributaries is usually considered a secondary treatment in addition to saphenous ablation (simultaneous, or in a second stage). As phlebectomies alone affect the hemodynamics of the venous system, this treatment can be effective as primary intervention in selected cases.

We found that treatment with single phlebectomies of a large varicose tributary leads to elimination of GSV reflux in 50% of patients and to relieve of symptoms in 66% of patients. We concluded that phlebectomies as a single treatment can be effective in patients with limited varicose vein disease. Different predictors of success were determined and a prediction model with score chart was made. This model can be used to assist in deciding for which patient phlebectomies can be used as first step treatment.

In Chapter 6 we review the available literature on varicose vein recurrence after endovenous treatments. Several etiologies were recognized: tactical and technical failure of treatment, progression of varicose disease, neovascularisation, and recanalisation of a previously obliterated vein. The first studies with 5-year follow-up of endovenous laser ablation are finally published, providing information on long-term efficacy and recurrences. Long term follow-up of the MAGNA trial will contribute on the knowledge of the recurrence rates and types of the three most used treatments for varicose veins, being CS, EVLA, and UGFS.

In Chapter 7, we address the difficult discussion on treatment indications for varicose veins and the reimbursement of varicose vein treatment by health insurance companies. We discuss the different treatment options and their effectiveness in terms of occlusion and secondary outcomes. We argue that secondary outcomes such as patient reported outcomes should play a more important role in deciding about the best treatment option. Furthermore, we discuss the theory of the ascending etiology of varicose vein in light of the positive hemodynamic results after phlebectomies. We conclude this chapter by advocating to treat the individual patient, some patients are better off when the cause of ascending varicose disease is treated (i.e., tributary treatment) whereas others are better off treated with the opposite approach, such as a combination of saphenous and tributary treatment.

SAMENVATTING

Hoofdstuk 1 is de algemene introductie van dit proefschrift. Veneuze insufficiëntie van de benen komt veel voor en de incidentie neemt toe met de leeftijd. Chronische veneuze insufficiëntie (CVI) heeft grote impact op de gezondheid gerelateerde kwaliteit van leven van patiënten en leidt tot hoge gezondheidskosten. Varices (spataderen) zijn een belangrijk onderdeel van veneuze insufficiëntie. De standaard behandeling voor insufficiëntie van de Vena Saphena Magna (VSM) was meer dan honderd jaar chirurgische ligatie van de saphenofemorale junctie met of zonder stripping. Rond het jaar 2000 werden meerdere minimaal invasieve behandelmethoden geïntroduceerd om de effectiviteit, gezondheid gerelateerde kwaliteit van leven en tevredenheid over de behandeling te verbeteren. Bijkomende voordelen van deze behandelingen zijn het gunstige bijwerkingenprofiel, lagere kosten en minder postoperatieve pijn. Het hoofdstuk eindigt met de motivatie en doelen van dit proefschrift.

In Hoofdstuk 2 wordt een overzicht gegeven van de verschillende minimaal invasieve behandelmogelijkheden. Klassieke chirurgie heeft een relatief hoge recidiefkans, op het ontstaan van recidief, een iets hogere kans op complicaties en het postoperatieve herstel duurt langer. Om dit soort nadelen te verminderen werden verscheidene minimaal invasieve methoden ontwikkeld. Deze nieuwere behandelmethoden dagen de chirurgische methode uit om als standaard behandelmethode voor patiënten met varices ingezet te worden. Echogeleide sclerocompressie therapie (ESCT), endoveneuze laser ablatie (EVLA) en radiofrequente ablatie (RFA) zijn de meest gebruikte endoveneuze methoden. In dit overzicht informeren we behandelaars over de therapeutische opties voor ablatie van saphene varices en beschrijven en vergelijken we de indicatie, de procedures, de effectiviteit en de veiligheid van bovenbeschreven behandelmethoden.

Hoofdstuk 3 beschrijft verschillende instrumenten die gebruikt kunnen worden om patiënt gerapporteerde resultaten te evalueren. Er zijn generieke en ziektespecifieke vragenlijsten beschikbaar. Het is niet verwonderlijk dat patiënten met CVI een verlaagde ziektegerelateerde kwaliteit van leven hebben door de aanwezigheid van varices, en de symptomen, gevolgen en complicaties van CVI. Verschillende studies bevestigen dat patiënten na behandeling een verbetering van hun kwaliteit van leven ervaren. In aanvulling op generieke gezondheidsgerelateerde vragenlijsten, zoals de Short Form (36) Health Survey (SF-36) en de EuroQual-5D, die gebruikt zijn bij patiënten met CVI, kunnen ziektespecifieke instrumenten meer informatie geven over de impact van CVI en varices op het dagelijks leven van de patiënt. De drie meest gebruikte ziektespecifieke instrumenten zijn de Aberdeen Varicose Vein Questionnaire (AVVQ), de Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) en de VEINES Sym/QoL. Deze vragenlijsten geven alle op een andere wijze specifieke informatie en kunnen voor verschillende onderzoeksdoeleinden gebruikt worden. Tot heden was alleen de AVVQ vertaald in en gevalideerd voor de Nederlandse taal. In dit hoofdstuk vertalen en valideren we de CIVIQ en de VEINES Sym/QoL in twee separate studies voor Nederlandse

patiënten met varices. Verschillende psychometrische parameters werden getest in de heterogene groep patiënten die werden behandeld voor varices. We concluderen dat beide gevalideerde vragenlijsten gemakkelijk en betrouwbaar zijn voor gebruik.

Hoofdstuk 4 beschrijft de resultaten van de *MAGNA-trial*. In deze gerandomiseerde klinische studie worden anatomisch succes, complicaties en verbetering in gezondheidsgerelateerde kwaliteit van leven vergeleken tussen EVLA, ESCT en conventionele chirurgie voor de behandeling van primaire VSM insufficiëntie. Na een jaar bleek het anatomisch succes gemeten met echo duplex van EVLA en conventionele chirurgie vergelijkbaar en bleken beide beter dan ESCT. Alle behandelingen bleken veilig, er waren geen ernstige complicaties. Wondinfecties en neovascularisatie werden alleen gezien in de patiëntengroep die behandeld was met conventionele chirurgie. Alle behandelingen resulteerden in een significante verbetering van klinische en patiëntgerapporteerde kenmerken. Lange termijn effect van deze behandelmethoden zal nog geanalyseerd worden uit de 5-jaars resultaten.

Hoofdstuk 5 beschrijft de resultaten van een prospectieve observationele studie, waarbij het effect van flebectomie op reflux in de VSM wordt geëvalueerd. Flebectomie wordt meestal gezien als aanvullende behandeling en wordt meestal tijdens of na behandeling van de stam verricht. Eerdere studies hebben reeds aangetoond dat flebectomie alléén óók effect kan hebben op de hemodynamiek van het veneuze systeem. Deze behandeling kan daarom ook effectief zijn als primaire behandeling in een geselecteerde patiëntengroep.

De studie wees uit dat behandeling met alleen flebectomie van een forse zijtak op het bovenbeen effectief was om reflux van de VSM te laten verdwijnen in 50% van de patiënten. Bij 66% van de patiënten verdwenen de klachten volledig. Flebectomie kan een effectieve behandeling zijn in patiënten met beperkte veneuze afwijkingen. Verschillende predictoren voor succes werden gevonden en met behulp van deze predictoren werd een predictie model en score chart gemaakt. De score chart kan gebruikt worden om te beslissen welke patiënt profijt kan hebben van een behandeling met flebectomie alleen en bij wie het beter is de stam en de zijtak tegelijk te behandelen.

In Hoofdstuk 6 maken we een samenvatting van de beschikbare literatuur over het ontstaan van recidieven na endoveneuze behandelingen. Recidieven komen voor na alle behandelingen van varices. Er wordt onderscheid gemaakt tussen een residu door een technische fout, neovascularisatie na ligatie en stripping, revascularisatie na EVLA en ESCT en recidiefvorming door voortgang van ziekte. De eerste studies met 5 jaar follow up na endoveneuze laser ablatie zijn gepubliceerd. Lange termijn resultaten van de *MAGNA-trial* zullen bijdragen aan de kennis over het type en de frequentie van recidieven na EVLA, ESCT en CS.

Hoofdstuk 7 is de algemene discussie van dit proefschrift. In dit laatste hoofdstuk worden de indicatiestelling voor de behandeling van varices en de vergoedingsregelingen van de zorgverzekeraars aangekaart. We bediscussiëren de verschillende behandelopties en

richten ons daarbij op de effectiviteit uitgedrukt in occlusie en secundaire uitkomsten. We beargumenteren waarom het belangrijk is om patiënt gerapporteerde kwaliteit van leven scores te implementeren om te beslissen welke behandeling het meest aangewezen is. Dit hoofdstuk eindigt met de aanbeveling voor iedere patiënt een individueel behandelplan op te stellen, gebaseerd op meerdere parameters en niet alleen op anatomische of hemodynamische afwijkingen, zoals reflux.

Chapter 9

Dankwoord
List of co-authors
List of publications
Curriculum Vitae
PhD Portfolio

Dankwoord

Promoveren kun je niet alleen. Men zegt dat je tijdens een zwangerschap 8% minder hersenfunctie hebt, hopelijk vergeet ik hierdoor geen personen te bedanken. Mocht dit toch gebeuren, dan bij deze mijn grote dank aan diegene die ik niet persoonlijk benoem! Graag wil ik een aantal mensen in het bijzonder bedanken, die mij de afgelopen jaren hebben geholpen deze mijlpaal te behalen.

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De Maeseneer MG, **Biemans AA**. Comment on: 'Great Saphenous Vein Diameter at the Saphenofemoral Junction and Proximal Thigh as Parameters of Venous Disease Class'. Eur J Vasc Endovasc Surg 2013 Apr 26 (Epub ahead of print)

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Biemans AA, De Maeseneer MGR. Results of the MAGNA trial, a randomized controlled trial comparing endovenous laser ablation, ultraguided foam sclerotherapy and conventional surgery in patients with varicose veins. Extended abstract. Vasomed 2013. Submitted.

Curriculum Vitae

In 1980 werd Anke Adriana Maria Biemans geboren op tweede kerstdag (26-12-1980) te Boekel, een klein dorp in de Peel (Noord-Brabant). Zij behaalde het Atheneum op het Kruisheren Kollege te Uden in 1999 en startte in datzelfde jaar de studie Geneeskunde aan de Radboud Universiteit te Nijmegen. In de laatste fase van de studie werkte en reisde zij een half jaar in de armste gebieden van Midden-Amerika. Tijdens haar studie groeide de interesse voor praktische vakken, met voorkeur van superficiële chirurgie. Met de gedachte chirurg te worden startte zij na het artsexamen in 2006 als ANIOS in het Catharina Ziekenhuis te Eindhoven. Zij werkte achtereenvolgens een jaar op de intensive care en een jaar op de algemene chirurgie. Tijdens deze werkzaamheden kwam zij in contact met het vak dermatologie en besloot ze om haar hart te volgen. Zij werkte een jaar als ANIOS dermatologie alvorens zij in 2009 startte met de opleiding tot dermatoloog in het Erasmus MC te Rotterdam. Haar opleiding combineerde ze met dit promotie onderzoek. Anke woont sinds 2006 in Eindhoven en is in 2010 getrouwd met John Mennen. In 2011 werd hun geluk verdubbeld door een zoon, Milan. Op dit moment is een tweede kindje op komst. Naar verwachting volbrengt zij begin 2014 de opleiding en zal zij gaan werken in de regio Noord Brabant.

PhD Portfolio

Summary of PhD training and teaching activities
Name PhD student: Anke A.M. Biemans
PhD period: March 2008 – Septembre 2013
Erasmus MC Department: Dermatology
Promotors: Prof.dr. T. Nijsten, Prof.dr. H.A.M. Neumann
Supervisor: Dr. R.R. van den Bos

	Year	Workload (Hours/ ECTS)
1. PhD training		
General academic skills		
– DOO Samenwerken	2009	1 ECTS
– DOO Ethiek	2010	1 ECTS
– Dermatosurgery Basic surgical skills	2010	0,5 ECTS
– Duplex Cursus, EMC Rotterdam	2010	1 ECTS
– DOO Communicatie	2011	1 ECTS
– Superficial Surgery and Anatomy, San Diego	2012	4 ECTS
– Teach the teacher, EMC	2012	1 ECTS
– Biomedical English Writing and Communication, EMC	2012	2 ECTS
– Workshop Endnote (online)	2012	0,5 ECTS
Research skills		
– Masterclass: onderzoeksvaardigheden, Brabant Medical school	2008	2 ECTS
– Masterclass: Medical Writing, Brabant Medical School	2008	1 ECTS
– BROK (Basis Registratie Onderzoek Klinische Trails)	2011	1 ECTS

Presentations		
– Congres Cabourg III, Frankrijk. 'Kwaliteit van leven en validatie van vragenlijsten.'	2009	1 ECTS
– MFO Rotterdam. 'Superficial thrombophlebitis of the venous dorsal arch of the foot and deep venous thrombosis after foam sclerotherapy.'	2009	1 ECTS
– MFO Rotterdam. 'Richtlijn bespreking DVT.'	2009	1 ECTS
– MFO Rotterdam. 'Zin en onzin van antistolling bij EVLA.'	2009	1 ECTS
– MFO Rotterdam. 'Randomized clinical trial of different bandage regimens after foam sclerotherapy for varicose veins.'	2009	1 ECTS
– Bijeenkomst Huidfonds, Rotterdam. 'Recente ontwikkelingen in de spataderwereld'.	2010	1 ECTS
– MFO Rotterdam. 'Validation of the CIVIQ in Dutch patients treated for varicose veins.'	2010	1 ECTS
– MFO Rotterdam. 'Resultaten van de MAGNA trial.'	2012	1 ECTS
– Wetenschappelijke vergadering NVDV, Rotterdam. 'MAGNA trial 1e jaars resultaten'.	2012	1 ECTS
– Vascular Rounds cluster Heelkunde, EMC Rotterdam. "Resultaten van de MAGNA trial".	2012	1 ECTS
– Beneluxvergadering, Brugge. 'Results of the MAGNA trial'	2012	1 ECTS
– Cabourg IV, Frankrijk. 'Effect of phlebectomy on reflux of the GSV.'	2013	1 ECTS
– Benelux vergadering, Oisterwijk. 'Effect of phlebectomy on reflux of the GSV.' (first price)	2013	1 ECTS
International conferences		
– European Vascular Course, Amsterdam (15-17 may)	2008	1 ECTS
– European Vascular Course, Maastricht, the Netherlands (25-27 febr).	2009	1 ECTS
– 4th Mediterranean meeting of venous disease, Nice (28-29 may)	2010	1 ECTS
– Benelux vereniging, Brugge, Belgium (1-2 jun)	2012	1 ECTS
– Benelux vereniging, Oisterwijk, The Netherlands (31 may- 1 jun)	2013	1 ECTS
2. Teaching		
Seminars and workshops		
– Workshop Ambulante Compressie Therapie	2009	1 ECTS
– ICK onderwijs Flebologie	2011	1 ECTS