Simone Katinka van der Velden

Management Strategies in Patients with Chronic Venous Disease

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Management Strategies in Patients with Chronic Venous Disease

Behandelingsstrategieën bij patiënten met chronische veneuze ziekte

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Simone Katinka van der Velden
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Promotor:	Prof.dr. T.E.C. Nijsten
Leescommissie:	Prof.dr. P.J.E. Bindels Prof.dr. J.M. Hendriks Prof.dr. Ph.I. Spuls
Copromoteren:	Dr. M.G.R. De Maeseneer Dr. R.R. van den Bos

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CHAPTER 1

General introduction

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BACKGROUND

Chronic venous disease (CVD) is defined as any morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and care.[1] Symptoms traditionally ascribed to CVD include sensation of throbbing or heaviness, leg-tiredness and/or fatigue, muscle cramps, swelling, aching, burning, tingling and restless legs syndrome, as well as esthetic concerns. Clinical manifestations of CVD are telangiectasia, reticular veins, varicose veins, edema, skin changes (pigmentation, eczema, lipodermatosclerosis, atrophie blanche) and venous ulcers. Patients with CVD, and especially those with venous leg ulcers, may experience considerable discomfort, disability and a reduced quality of life.[2]

CVD is highly prevalent in the western world. About 20-25% of the population suffers from varicose veins.[3] Chronic venous insufficiency (CVI) is a term reserved for advanced CVD, resulting in edema, skin changes or venous ulcers. It is reported in 8-16% of the population, but only 1% will develop a venous leg ulceration.[3] Prevalence of CVI is slightly higher in males than in females and is increasing with age.[4-6]

CVD has a considerable socio-economic impact, mainly because the care for patients with venous leg ulceration is very expensive.[7] In the Netherlands, with an ever ageing population, healthcare expenses for CVD have increased to approximately 1.5% of the national healthcare budget (i.e., one billion euros annually).[8]

PATHOPHYSIOLOGY

The return of venous blood flow from the legs is highly dependent on several factors, including; the calf muscle pump, the venous valves, the venous tonus and the arterio-venous pulse pump.[9] Superficial venous reflux, defined as reversed flow during more than 0.5 seconds, occurs when the integrity between these factors is interrupted. The increased venous filling pressure results in wall stress and activation of venous endothelial cells and smooth muscle cells, inducing remodeling of the venous wall.[10] The venous hypertension is transmitted from the saphenous veins to the microcirculation, resulting in dilated capillaries with microthrombi and an increased capillary filtration of plasma proteins, leukocytes and erythrocytes. Subsequently, interstitial edema, trapping of enzymes and finally a decreased diffusion of oxygen will occur.

Valve failure of the superficial veins may be primary, caused by pre-existing weakness in the vessel wall or in the valve cusps due to genetic predisposition. Different candidate genes have been linked to valve failure in various forms of CVD. For example, the single nucleotide polymorphisms in FOXC2 provide a strong association with valve failure.[11]

Alternatively, valve failure may be secondary to direct injury of the valve and vein wall by superficial vein thrombosis (SVT).

The muscle pumps in the foot and leg, and especially the calf muscle pump, play a very important role in the return of venous blood. When the calf muscles are no longer able to compensate the increased venous pressure in refluxing or obstructed veins, muscle pump dysfunction occurs. Gradual weakening and atrophy of the calf muscle in elderly and primary neuromuscular disorders or disturbance of normal ankle movement may also cause muscle pump dysfunction.[6,12]

Primary varicose veins develop as a result of venous dilatation and/or valve damage in the superficial venous system, without previous deep vein thrombosis (DVT). They differ from secondary varicose veins, which are caused by persisting reflux or obstruction in the deep venous system after DVT. Dysfunction of the valves of the deep venous system causes deep venous reflux, which in turn may induce secondary superficial venous reflux and visible varicose veins. On the other hand, residual obstruction of the deep venous system leads to development of collateral veins, which may exactly look like varicose veins.

Superficial venous disease in saphenous trunks (STs) and tributaries can either start at the level of a connecting point (junction) between the deep and superficial venous system (saphenofemoral junction [SFJ], saphenopopliteal junction [SPJ] or perforating veins) or at the level of the tributaries.[13-15] Two pathophysiological concepts can be distinguished. The first concept of reflux origin is also known as the classic 'descending' theory (e.g., reflux starts at the level of the junction into the ST and further into the tributaries); the second concept is based on the multifocal 'ascending' theory (e.g., reflux starts at the level of the tributaries and progresses towards the ST and eventually to the junction) (Figure 1). When treating patients with CVD, physicians need to be aware of both these concepts.

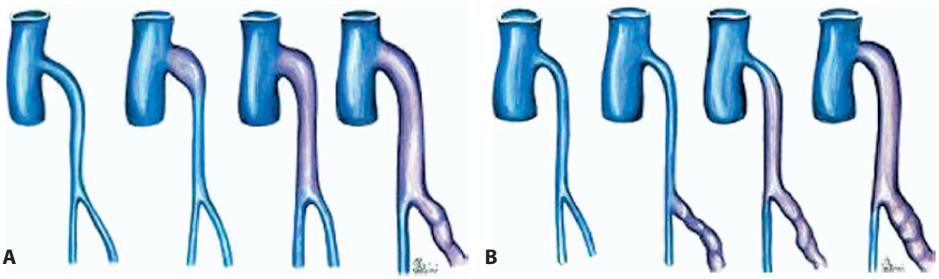

Figure 1. Progression of varicose changes according to the descending (A) and ascending (B) theory. Figure adapted from *Caggiati et al. J Vas Surg 2006.*

RISK FACTORS

There are several risk factors associated with CVD including age, gender, family history of varicose veins, pregnancy, obesity, prolonged standing and previous SVT or DVT.[16-19] In elderly patients, weakening of calf muscles and deterioration of the vessel wall may contribute to the development of CVD.[20] Excess weight as well as pregnancy results in a relative obstruction of the venous return, leading to increased hydrostatic pressure in the legs. Also, the likelihood of developing varicose veins or CVI increases with the number of pregnancies.[21,22] Non-Hispanic whites probably have a higher risk for developing CVD than other ethnicities.[23]

CLINICAL PRESENTATION

Clinical findings in patients with CVD are usually classified according to the CEAP classification for chronic venous disorders, defining the clinical (C), etiologic (E), anatomic (A), and pathophysiologic (P) details in an affected limb.[24] The 'C' of the CEAP classification distinguishes seven clinical classes labelled from C0 to C6: no visible signs of CVD (C0), telangiectasia or reticular veins (C1), varicose veins (C2), venous edema (C3), skin changes (C4) - subdivided into pigmentation or eczema (C4a), and lipodermatosclerosis or atrophie blanche (C4b) -, healed venous ulcer (C5), and active venous ulcer (C6). Corona phlebectatica, defined as the fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot, is categorized as C1, although this clinical sign may be an early sign of more advanced CVD.[25]

CEAP is a descriptive classification and cannot be used as a scoring system. Therefore, in 2000, a venous severity scoring system has been developed as a tool to measure disease severity. This tool includes three components: the Venous Disability Score, the Venous Segmental Disease Score, and the Venous Clinical Severity Score (VCSS). The VCSS comprises ten items regarding symptoms and clinical signs; each of these is rated on a four-point scale (from 0 to 3).[26]

In addition to venous symptoms and signs, patients with CVD may also present with acute complications such as SVT and/or DVT and in rare cases, with acute varicose vein bleeding.

DIAGNOSIS

Duplex ultrasound (DUS) is considered the gold standard for investigation of the lower limb venous anatomy and hemodynamics. Venous DUS combines B-mode imaging with

pulsed wave and color Doppler assessment of flow direction, and it is used to assess the etiology, anatomy and pathophysiology of CVD. Patients should be examined in standing position to standardize preoperative and postoperative measurements of venous diameters and reflux.[27,28]

In patients with CVD, venous pathology may involve the junctions (SFJ or SPJ), STs (e.g., great saphenous vein [GSV], anterior accessory saphenous vein [AASV], posterior accessory saphenous vein [PASV], small saphenous vein [SSV] or thigh extension of the SSV/ Giacomini vein), their tributaries or their perforating veins, or a combination of the above. Reflux in the superficial venous system is defined as retrograde flow for more than 0.5 seconds following Vasalva manoeuvre (only for evaluation of the SFJ) and/or manual calf or foot squeeze. Other methods to elicit reflux are: manual compression of vein clusters, pneumatic cuff deflation and active foot dorsiflexion and relaxation.[29] In patients presenting with symptoms and signs of CVD, reflux of the GSV is the most common hemodynamic abnormality.[30]

Venous function can also be evaluated with air phlethysmography, photoplethysmography, strain gauge plethysmography or foot volumetry.[31] Ambulatory venous pressure monitoring is the gold standard for assessing the hemodynamics of CVD.[12] Venography, Computed Tomographic Venography and Magnetic Resonance Venography are proper techniques to assess complex venous anatomy by using intravenous contrast agents. In addition, intravascular ultrasound has been introduced to visualize intraluminal anatomy.[12]

TREATMENT

There are numerous options for the management of CVD, of which the most important are listed below.

Endovenous thermal ablation

In agreement with recent guidelines, endovenous thermal ablation (EVTA) is nowadays commonly used to treat a refluxing ST.[31-34] The most commonly used EVTA methods are endovenous laser ablation (EVLA), radiofrequency and steam ablation. All EVTA techniques can be performed under local tumescent anesthesia. The vein is entered under ultrasound-guidance and a laser fibre or other ablation catheter is introduced in the ST. The tip of the ablation device is usually positioned at 1 to 2 cm below the SFJ or SPJ. Subsequently tumescent anesthesia is administered under ultrasound-guidance. While withdrawing the laser fibre or catheter, energy is emitted intraluminally, causing irreversible thermal damage of the vein wall. The induced thermal injury causes destruction of the endothelium, denaturation of collagen in the media and subsequent thrombosis and fibrosis of the vein.[35]

Non-thermal non-tumescent techniques

Recently, non-thermal techniques, not requiring tumescent anesthesia, have been developed. Mechanochemical ablation combines mechanical injury of the intima with concomitant infusion of a liquid sclerosans through the distal end of the catheter. Another technique is cyanoacrylate glue ablation, which uses cyanoacrylate adhesive. A small amount of glue is injected stepwise through an intravascular catheter to seal the vein.[33]

Foam and liquid sclerotherapy

Injection of sclerosant solution can be applied in its liquid form, or mixed with air or physiologic gas to obtain sclerosant foam. It may be used in legs with telangiectasia, refluxing tributaries and refluxing STs. Injection of a sclerosans causes destruction of venous endothelial cells, exposure of subendothelial collagen fibres and finally fibrotic obstruction.

In the Netherlands, only one slerosant solution is available: polidocanol.[36] This is available in different concentrations ranging from 0.5% to 3% and can be used both as liquid and foam. To obtain foam, 1 mL of sclerosant is mixed with 3 or 4 mL of air using the Tessari method.[37] The foam is usually injected under ultrasound-guidance and therefore the technique is often called 'ultrasound-guided foam sclerotherapy'. Foam is more effective than liquid sclerosans because of its longer contact time with the venous wall and its increased surface area with the venous wall, resulting in immediate spasm of the ST.

Surgery

Until the end of the last century, varicose vein surgery mainly consisted of high ligation and stripping of the refluxing trunk (HL/S) in combination with phlebectomies of varicose tributaries. Nowadays several other less invasive surgical techniques are available such as ambulatory phlebectomy (AP), stripping without high ligation, and the CHIVA method (a French acronym for 'Cure conservative et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire').

HL/S consists of ligating the refluxing ST at the SFJ or SPJ with a non-absorbable suture, after ligation of all tributaries near the junction, and invaginating stripping of the ST. With the introduction of local tumescent anaesthesia, traditional HL/S has involved towards a less invasive technique.[31,32]

AP is performed under local or local tumescent anaesthesia in an outpatient setting. Small stab incisions are made over varicose tributaries usually with a No.11 blade. The veins are exteriorized through the incision using a phlebectomy hook or mosquito.[31,32] AP can be performed as a single treatment of varicose tributaries not connected to a refluxing ST or it may be a primary procedure for treating varicose veins with the aim of preserving the ST.[31,31] The latter procedure is also known as the ASVAL method (Ambula-

tory Selective Varices Ablation under Local anaesthesia) and is based on the concept of ascending or multifocal evolution of varicose veins.[38] AP may also be performed as adjunctive treatment after EVTA or non-thermal ablation of the refluxing ST, in the same or a subsequent treatment session.

The main goal of the CHIVA method is to decrease the hydrostatic pressure in the ST and tributaries by ligating specific areas in the superficial venous system.[31,32] Thereby the ST and venous drainage into the deep system is preserved. It is not a very widespread method and is mainly performed by specialists in the field of CHIVA.

Compression therapy

Compression therapy is an important adjunct to superficial venous ablation in patients with CVD and is recommended as first line therapy for those with venous ulcers.[31,32] Elastic and non-elastic garments compensate the increased ambulatory venous pressure in advanced CVD and improve the microcirculation, resulting in reduction of edema and symptoms. Intermittent pneumatic compression devices are also used in patients with refractory edema and venous ulcers.[31,30]

PERSONALIZED MEDICINE

Phlebology has long been a field lacking proper scientific background, but in the last 10-15 years, major steps forward have been made. Several dozens of randomized controlled trials (RCTs) have now been published resulting in an evidence-based medicine (EBM) approach. This has led to numerous effective treatment possibilities for patients with varicose veins and more advanced stages of CVD. The modern phlebologist can now use different tools to treat a patient and this has made the management of CVD complex and controversial. On the other hand, having many valuable treatment options may also be very beneficial for the individual patient, for which patient-tailored treatment, also known as personalized medicine, has now become available.

Although an overall superiority of EVTA has been clearly established,[31-34] not all patients can be treated in the same way. It may well be that alternative treatments are a better option for a particular patient or subgroups of patients. In addition, a better stratification of patients by disease severity or expected response to treatment could optimize care and may also result in substantial cost savings for the health care system.

The concept of personalized management decisions has been implemented in several areas of medicine. However, in order to optimize personalized medicine in phlebologic practice, algorithms for CVD management should be developed. Thereby, findings resulting from EBM should be translated into a more 'cookbook approach' of the particular situation of an individual patient.

Combining current scientific evidence with expert opinion may eventually result in a more personalized approach. Treatment recommendations were initially based on expert opinions. However, in the last 20 to 30 years, the EBM approach based on high quality RCTs, pooling and summarizing data, has replaced to some extent the expert opinion. Interestingly, one of the drawbacks of EBM is that it does not fully take patient characteristics into consideration. To include these specific circumstances, expert opinions are required again, completing the circle (Figure 2).

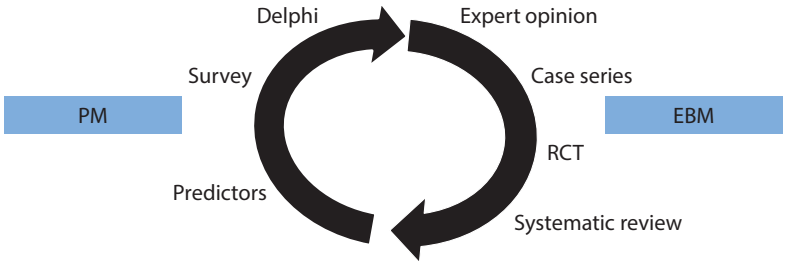

Figure 2. Cycle of evidence
Abbreviations: EBM, evidence-based medicine; RCT, randomized controlled trial; PM, personalized medicine

AIMS OF THIS THESIS

The aim of this thesis was to develop an algorithm for personalized management decisions in patients with CVD (C2-C6). In order to do so, we first aimed to investigate the specificity of venous symptoms for the diagnosis of CVD, because presence of venous symptoms is an important criterion to decide whether or not to treat a patient (**chapter 2**).

Our second aim was to evaluate the durable effects of three frequently used treatment techniques (i.e., HL/S, EVLA and UGFS) because current phlebologic EBM is largely based on short- or mid-term follow-up studies (**chapter 3**).

Our third aim was to assess the elasticity of the ST by assessing diameter change between standing and lying position, which we called postural diameter change (PDC) of the ST (**chapter 4**). The degree of PDC might become a useful additional tool to estimate severity of CVD and may help physicians to decide whether or not to ablate the ST in a particular patient with CVD. In chapter 4, we also reported our research on properties of the ST by studying focal dilatations of the ST and their association with patient and DUS variables.

Our fourth aim was to determine patient, DUS and device specific predictors for recanalization following EVTA (**chapter 5**).

Our final aim was to evaluate how patient and DUS related variables influence treatment strategies in CVD patients (C2-C6) and eventually introduce a management strategy algorithm (**chapter 6**). Ideally, the results of this thesis should contribute to the improvement of personalized medicine in phlebologic practice.

I hope you will enjoy reading my thesis.

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CHAPTER 2.1

Translation and validation of the Dutch VEINES-QOL/Sym in varicose vein patients

van der Velden SK
Biemans AA
Nijsten T
Sommer A

Phlebology 2014;29(4):227-35.

ABSTRACT

Objectives: To translate from English to Dutch and evaluate the psychometric properties of the VEnous INsufficiency Epidemiological and Economic Studies (VEINES) questionnaire, divided into 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, CEAP (Clinical Etiologic Anatomic Pathophysiologic) 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. If 5% or more of the responses were missing, feasibility of the individual items was considered poor. 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-eight 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 0.9 and 0.8, respectively). The VEINES-QOL demonstrated a good construct validity for the physical component of the SF-36, but not for the mental component (rho = 0.6 and 0.2, respectively), as expected. The VEINES-Sym correlated poorly with both SF-36 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 for the evaluation of therapies in patients with varicose veins.

INTRODUCTION

Chronic venous disease (CVD) is 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. These measures are developed to use across many different diseases and therefore they are less precise and sensitive 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 the VEnous INsufficiency Epidemiological and Economic Studies (VEINES) questionnaire.[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 (e.g., physical, psychological, social impairments and level of pain).[5] The 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, 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]

Our 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 14-years-old in consideration. The forward translations were performed by the principal investigator (SvdV) 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. Those responsible for the forward translation and an independent dermatologist reviewed the backward translation for conceptual equivalence with the original English version. If necessary, adaptions 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 CVD. 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 at the outpatient Department of Dermatology (Maastricht University Medical Center) 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 superficial venous reflux (retrograde flow during more than 0.5 seconds) was found during duplex 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 legs that were classified according to the clinical component of the international accepted CEAP (Clinical Etiologic Anatomic Pathophysiologic) classification.[10] Venous signs, such as telangiectasia, reticular veins, varicose veins, edema, skin changes (hyperpigmentation and lipodermatosclerosis) or

ulcerations were recorded. Subsequently, duplex ultrasound examination of both the superficial and deep venous systems was performed in standing position.[11]

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 eight different dimensions 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) (Supplementary Figure 1). Two summary scores can be computed; the VEINES-Sym score which reflects the extent of venous symptoms and the 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 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 this component and thereby sharing 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 was considered good, if values were 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-36. 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 *versus* C2 *versus* C3-C6) should have a statistically significantly higher impact on HRQoL, which was tested using an analysis of variance.

The distribution of the data was presented as mean with standard deviation (SD) or median with interquartile range values as appropriate. Categorical data were analyzed by means of χ^2 test or, if necessary, Fisher's exact test. Two-sided *p*-value of < .05 were considered statistically significant. All analyses were conducted using SPSS (SPSS Inc., Chicago, IL, USA). The medical ethical committee of the University Hospital Maastricht (The Netherlands) granted exempt status for this observational study.

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 (3%).

Of the 66 participants, 74% were women and the mean age of the study population was 54.9 years (SD 13.1, range 20-81 years; Table 1). 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'.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Sex	
Males	17 (26)
Females	49 (74)
Age in years, mean (SD, range)	54.9 (13.06, 20-81)
CEAP classification	
C1	23 (35)
C2	22 (33)
C3	17 (26)
C4	3 (5)
C5	0
C6	1 (1)
Perforating veins	0
Deep system (femoral vein)	2 (3)
No reflux	19 (29)
Reflux	47 (71)

Abbreviation: SD, standard deviation; CEAP, Clinical Etiologic Anatomic Pathophysiologic classification

Feasibility

None of the individual items were considered suboptimal as missing responses varied between 0% and 5%. However, item 1.9 ('tingling sensation') and item 4b ('daily activities at home') were both missing in 5% of the participants, suggesting borderline feasibility of these items.

Out of the 25 items in the questionnaire, two demonstrated a substantial ceiling effect with 76% and 76% 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').

Structure

VEINES-Sym

All nine VEINES-Sym items loaded higher than the cuff-off value of 0.40, suggesting that these items fit the unidimensional structure of the VEINES-Sym. The loadings varied between 0.46 and 0.71 (Table 2).

VEINES-QOL/Sym

Twenty out of 25 items loaded higher than the cut-off 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 0.29, 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.

Table 2. 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	0.61	0.54
1.2 Aching legs	0.73	0.59
1.3 Swelling	0.46	0.38
1.4 Night cramps	0.49	0.43
1.5 Burning	0.64	0.52
1.6 Restless legs	0.65	0.50
1.7 Throbbing	0.63	0.58
1.8 Itching	0.46	0.40
1.9 Tingling	0.68	0.55
7 Pain	0.71	0.62
3 Evolution of the leg problem		0.31
4a Limitation of activities at work		0.56
4b Limitations of activities at home		0.79
4c Limitations of standing activities		0.68
4d Limitations of sitting activities		0.66
5a Less time spent on work or activities		0.75
5b Accomplished less		0.76
5c Limited in the kind of work or activities		0.56
5d Difficulty performing the work or activities		0.67
6 Social activities		0.77
8a Concerned about appearance of the legs		0.29
8b Felt irritable		0.66
8c Felt a burden to your family or friends		0.55
8d Worried about bumping the legs		0.41
8e Choice of clothing		0.35

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

Reliability

The item responses of the VEINES-QOL and VEINES-Sym showed an excellent internal consistency (Cronbach's alpha of 0.9 and 0.8, respectively).

Validity

The VEINES-Sym was borderline moderately correlated with the physical component but poorly correlated with the mental component of the SF-36 (rho = 0.4 and rho = 0.1, respectively). As expected, the VEINES-QOL was strongly correlated with the physical component but poorly correlated with the mental component of the SF-36 (rho = 0.6 and 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 significantly affected by severity of varicose veins (C1, C2, C3-C6; $p = .8$ and $p = .41$, 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 HRQoL and symptom instrument showed a good acceptability, validity and high reliability. This study provided evidence for a high feasibility, since 24 out of 25 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 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 studies 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.g., impairment, disability and functioning). However, all three are important to determine HRQoL.[16–18]

We were not able to achieve significant differences between the clinical CEAP categories. The poor correlation between the VEINES-Sym and VEINS-QOL scores and the clinical class may be explained by the 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-C3 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 and 7), functioning (items 4, 5 and 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 with 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 an 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 VEINES-QOL/Sym were comparable with 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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SUPPLEMENTARY

Supplementary Figure 1. English VEINES-QOL/Sym questionnaire

1. During the past 4 weeks, how often have you had any of the following leg problems?

(check one box on each line)	**Every day**	**Several times a week**	**About once a week**	**Less than once a week**	**Never**
1. Heavy legs					
2. Aching legs					
3. Swelling					
4. Night cramps					
5. Heat or burning sensation					
6. Restless legs					
7. Throbbing					
8. Itching					
9. Tingling sensation (e.g. pins and needles)					

2. At what time of the day is your **leg problem** most intense? (check one)

1. On waking
2. At mid-day
3. At the end of the day
4. During the night
5. At any time of the day
6. Never

3. Compared to one year ago, how would you rate your **leg problem** in general now? (check one)

1. Much better now than once year age
2. Somewhat better now than one year ago
3. About the same now as one year ago
4. Somewhat wore now than one year ago
5. Much worse now than one year ago
6. I did not have any leg problem last year

4. The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much?

(check one box on each line)	**I do not work**	**YES, limited a lot**	**YES, limited a little**	**NO, not limited at all.**
a. Daily activities at work				
b. Daily activities at home (e.g. housework, ironing, doing odd jobs/repairs around the house, gardening, etc.)				
c. Social or leisure activities in which you are standing for long periods (e.g. parties weddings, taking public transportation, shopping, etc..)				
d. Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema, theatre, travelling, etc..)				

5. During the past 4 weeks, have you had any of the following problems with your work or regular daily activities as a result of your **leg problem**?

(check one box on each line)	**YES**	**NO**
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

6. During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbours or groups? *(check one)*

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

7. How much leg pain have you had during the past 4 weeks? *(check one)*

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

8. These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much time during the past 4 weeks-

(check one box on each line)	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. Have you felt concerned about the appearance of your leg(s)?						
b. Have you felt irritable?						
c. Have you felt a burden to your family or friends?						
d. Have you been worried about bumping into things?						
e. Has the appearance of your leg(s) influenced your choice of clothing?						

CHAPTER 2.2

How specific are venous symptoms for diagnosis of chronic venous disease?

van der Velden SK
Shadid NH
Nelemans PJ
Sommer A

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ABSTRACT

Objective: The objective of this case control study is to evaluate whether and which 'venous' symptoms are most characteristic for patients affected with chronic venous disease (CVD) and reflux compared to patients with other diseases of the legs without reflux (e.g., arthrosis, peripheral arterial disease, spinal disc herniation).

Methods: A cross-sectional study was performed to compare the frequency of venous symptoms among 76 patients with CVD and reflux and 74 patients with other diseases of the legs without reflux. The VEINES-Sym of the VEINES-QOL/Sym questionnaire was used to evaluate the frequency of symptoms. Demographic, clinical classification and duplex ultrasound findings were also noted.

Results: A total of 122 patients were included for analysis (response rate of 87%). Presence of venous symptoms was slightly more often reported in the CVD group than in the 'other' group, but differences were small and statistically non-significant. Severity of CVD as classified by the CEAP classification was not associated with higher proportions of patients reporting symptoms than in the 'other' group, except for swelling ($p = .016$) and itching ($p = .007$) in C3-C6 patients. The largest difference between the CVD and the 'other' group was observed for the time of the day at which symptoms were most intense; patients with CVD were more likely to experience symptoms at the end of the day ($p < .001$).

Conclusions: The small differences in prevalence of reported 'venous' symptoms between CVD patients and patients with other diseases of the legs suggest that these symptoms may be less specific for patients with CVD and refluxing veins than is usually assumed.

INTRODUCTION

Chronic venous disease (CVD) is a common health problem in Western countries affecting about one quarter of the adult population.[1] It is commonly assumed that this condition is associated with symptoms such as tingling, aching, burning, pain, muscle cramps, swelling, sensation of throbbing or heaviness, itching skin, restless legs, leg-tiredness and/or fatigue.

In daily practice, the presence of one or more venous symptoms, together with clinical and duplex ultrasound findings of venous disease is an indication for the treatment of varicose veins.

However, equivocal results from previous studies suggest that the association between CVD and venous symptoms may not always be that strong as is assumed and that these symptoms may also have a non-venous cause.[2,3] Furthermore, it has been observed that despite successful treatment of the refluxing saphenous trunk, reduction of symptoms such as restless legs, edema, cramps, pain and heavy or tired feeling, was reached in only part (40-83%) of the treated patients.[4-6] Alternatively, local recurrences of varicose veins or recanalized refluxing veins on duplex ultrasound are not always correlated with the presence of symptoms.[7,8] These observations raise the question to what extent venous symptoms are specific for patients with CVD and reflux.

The prevalence of CVD is increasing with age and in particular the older population is affected with CVD.[1] In this population, the relationship between symptoms and presence of reflux may be further obscured by the presence of other diseases of the lower limbs, such as hip or knee arthrosis (AR), peripheral arterial disease (PAD) or spinal disc herniation (SDH) which may cause comparable symptoms in the leg. The present study explores this issue by comparing the distribution of symptoms between a patient group with CVD and a patient group with other diseases of the legs. The underlying hypothesis was that the so-called venous symptoms (tingling, aching, burning, pain, muscle cramps, swelling, sensation of throbbing or heaviness, itching skin, restless legs, leg-tiredness and/or fatigue) are non-specific for patients with CVD. The secondary objective was to compare the mean number of symptoms, the mean symptom score and the time of the day at which symptoms were experienced as most intense.

METHODS

Patients

This study was performed in the outpatient clinics of Dermatology, Vascular surgery, Orthopaedics and Neurology at the Maastricht University Medical Center between November 2010 and June 2011. Eligible were patients older than 18 years visiting the

outpatient Department of Dermatology with one or more venous symptoms. Patients of the outpatient Departments of Vascular Surgery, Orthopedics or Neurology visiting because of complaints of the leg(s) due to PAD, knee or hip AR or SDH, respectively, were also eligible. Diagnosis was confirmed by ankle brachial index and arterial pulse-wave Doppler recordings, X-ray or Magnetic Resonance Imaging, respectively.

A trained physician examined patient's affected legs and classified them according to the clinical component ('C') of the CEAP classification.[9] Venous signs, such as telangiectasia, reticular veins, varicose veins, edema, skin changes (hyperpigmentation, lipodermatosclerosis) or ulceration were recorded. Subsequently, duplex ultrasound examination of both superficial and deep venous systems was performed in standing position.[10] All patients in the CVD group had to have symptoms of venous disease and confirmed saphenous trunk reflux (>0.5 seconds) on duplex ultrasound. Patients with other diseases of the legs (PAD, knee or hip AR or SDH) were excluded if saphenous trunk reflux >0.5 seconds on duplex ultrasound was observed. We hypothesized that patients affected with clinical classes C5 or C6 would report more symptoms than patients affected with C1-C4 disease.[11] However, in clinical practice, C5 or C6 disease is relatively rare in patients affected with varicose veins compared to the other clinical classes. Therefore, we aimed to include 20 patients with healed or active ulceration of the leg.

Patients gave written informed consent to participate in the study.

Questionnaire

Patients were asked to complete the VEINES-Sym of the VEINES-QOL/Sym questionnaire.[12] 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.

The VEINES-Sym is part of the VEINES-QOL/Sym questionnaire and measures symptom frequency and severity. The VEINES-Sym consists of ten items including nine venous symptoms (heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, tingling sensation) rated on a five-point scale of frequency (1=every day, 2=several times a week, 3=about once a week, 4=less than once a week, 5=never) and leg pain, rated on a 6-point scale of intensity (1=very severe, 2=severe, 3=moderate, 4=mild, 5=very mild, 6=none). In this study, we focused on these nine venous symptoms.

In addition, descriptive information concerning the time of the day at which the symptoms are experienced most intensely was recorded (e.g., on walking, at mid-day, at the end of the day, during the night, at any time of the day, never). Summary symptom scores (VEINES-Sym) were computed from these ten items. The presence of lower VEINES-Sym scores indicates more severe symptoms (range 0-100).

Statistical analysis

Patients were categorized into two groups according to the reported frequency of symptoms: 'every day', 'several times a week', 'about once a week', 'less than once a week' *versus* 'never'. Proportions and absolute numbers of patients who reported presence of a specific symptom were compared between patients with CVD and patients with other diseases of the legs using the χ^2 test. In an additional analysis, the subgroup of patients reporting a specific symptom 'every day' was compared to the subgroup of patients who experienced that specific symptom 'less than every day', 'several times a week' or 'less'.

Patients with missing scores on three or more items were excluded from the analysis. For patients with missing scores on one or two items, missing values were imputed by median values on the completed items reported by an individual. To calculate VEINES-Sym scores, raw scores were first transformed to *z*-score equivalents (mean 0; standard deviation [SD] 1), which then were transformed to T scores (mean 50, SD 10).[12]

All analyses were performed using SPSS (SPSS Inc., Chicago, IL, U.S.A.). Two sided *p*-values of < .05 were considered to indicate statistical significance.

RESULTS

Study population

Eligible were 76 CVD patients with confirmed reflux and 74 patients with PAD, AR, or SDH without reflux (26 PAD, 25 AR, 23 SDH) (Figure 1).

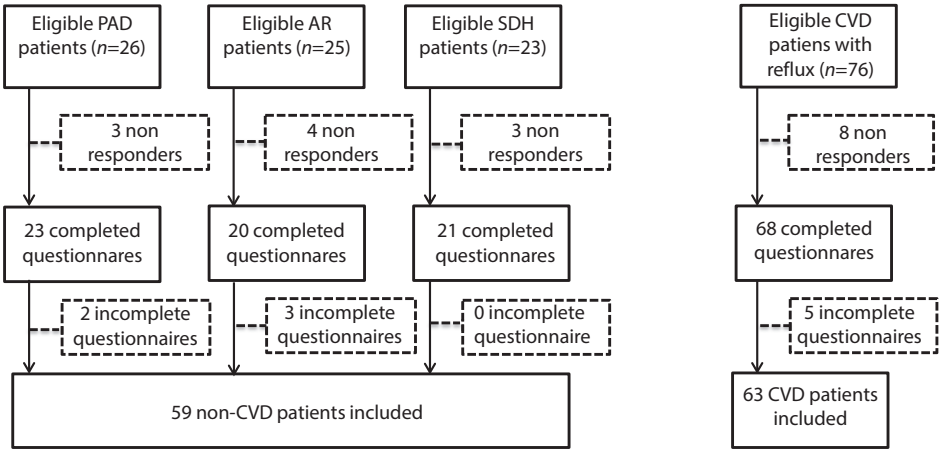

Figure 1. Flowchart.
Abbreviations: PAD, peripheral arterial disease; AR, arthrosis; SDH, spinal disc herniation; CVD, chronic venous disease.

A total of 132 patients completed the questionnaire. The response rate was 89% (68/76) in the CVD group and 86% (64/74) in the group with other diseases of the legs. Questionnaires were incomplete in 10 patients resulting in a total sample of 122 patients remaining for analysis.

Table 1 summarizes the distribution of baseline characteristics in the CVD group and the group with other diseases of the legs (PAD, AR, and SDH). It can be observed that 62% of the patients with CVD were female and the mean age was 61 years (SD 13, range 30-94; Table 1). In the 'other' group, half of the patients were female and the mean age was 59 years (SD 12, range 32-83). Five patients (8%) of the CVD group showed a combination of superficial and deep venous insufficiency. One patient only had deep venous insufficiency. In the CVD group, 57% had C3-C6, while in the group with other diseases of the legs this was only 7%.

Table 1. Distribution of patient characteristics.

	CVD, *n*(%)	**PAD, *n*(%)**	**AR, *n*(%)**	**SDH, *n*(%)**
Sex				
Male	24 (38)	13 (62)	4 (24)	13 (62)
Female	39 (62)	8 (38)	13 (76)	8 (38)
Age				
Mean	61	64	62	52
(SD, min- max)	(13, 30- 94)	(9, 45- 80)	(12, 36- 83)	(12, 33- 83)
Clinical classes				
C0	0	11 (52)	3 (18)	5 (24)
C1	7 (11)	5 (24)	12 (72)	13 (62)
C2	20 (32)	3 (14)	1 (5)	2 (10)
C3	16 (25)	2 (10)	1 (5)	1 (4)
C4	2 (3)	0 (0)	0 (0)	0 (0)
C5	1 (2)	0 (0)	0 (0)	0 (0)
C6	17 (27)	0 (0)	0 (0)	0 (0)
Reflux				
Superficial system	62 (98)	0 (0)	0 (0)	0 (0)
Perforating veins	1 (2)	0 (0)	0 (0)	0 (0)
Deep system	6 (10)	0 (0)	0 (0)	0 (0)

Abbreviations: CVD, chronic venous disease; PAD, peripheral arterial disease; AR, arthrosis; SDH, spinal disc herniation.

Presence of venous symptoms according to diagnosis

Seven out of nine symptoms (heavy legs, aching legs, swelling, night cramps, restless legs, itching, and tingling) were reported by more than 50% of the patients in the CVD group. This finding is in contrast to the patients in the 'other' group where only four out

of nine symptoms (heavy legs, aching legs, night cramps, and tingling) were reported by more than half of the patients (Figure 2). Higher proportions in the CVD group were observed for six symptoms: heavy legs (67% *vs* 61%), swelling (52% *vs* 31%), night cramps (71% *vs* 53%), restless legs (51% *vs* 47%), throbbing (40% *vs* 29%) and itching (52% *vs* 31%) (Table 2). However, no statistical significance was reached. Presence of aching legs, heat or burning sensation and tingling was reported by a higher proportion of patients in the 'other' group (Table 2).

When patients were categorized according to frequencies of symptoms 'every day' *vs* 'less than every day', the differences in proportions of patients between both groups increased only for aching legs (32% *vs* 49%, $p = .05$).

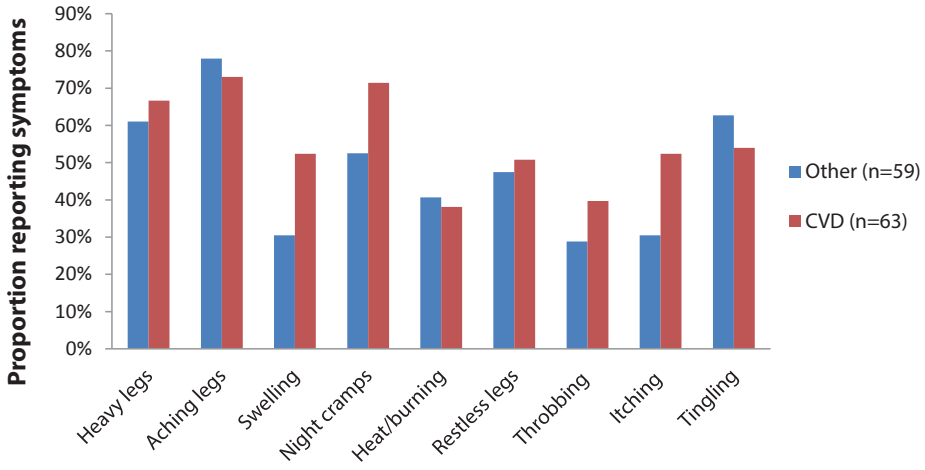

Figure 2. Presence of symptoms among patients with CVD and patients with other diseases of the legs (e.g., peripheral arterial disease, arthrosis and spinal disc herniation)
Abbreviation: CVD, chronic venous disease.

Clinical severity and presence of symptoms

Patients in the CVD group were categorized according to clinical classes (C1-C2 *vs* C3-C6) and these categories were compared with the 'other' group (Table 2). If only the CVD patients with clinical class C3-C6 were taken into consideration, the difference in proportion of patients with presence of symptoms between the CVD and 'other' group increased for the symptoms swelling, night cramps, throbbing and itching. In the latter comparison, statistically significant difference was reached for the symptoms swelling ($p = .02$) and itching ($p = .01$). When we categorized patients according to frequencies of symptoms 'every day' *vs* 'less than every day' the differences between the CVD with clinical class C3-C6 and 'other' group did not increase.

Table 2. Proportion of patients with symptoms among the group with 'other' diseases of the legs, and the CVD group (overall, C1-C2, and C3-C6)

	'Other' *n*=59	CVD all *n*=63	CVD (C1-C2) *n*=27	CVD (C3-C6) *n*=36
Heavy legs	61%	67%	70%	64%
Aching legs	78%	73%	74%	72%
Swelling	31%	52%	48%	56%
Night cramps	53%	71%	70%	72%
Heat/burning	41%	38%	37%	39%
Restless legs	47%	51%	59%	44%
Throbbing	29%	40%	30%	47%
Itching	31%	52%	44%	58%
Tingling	63%	54%	63%	47%

Other includes patients with other diseases of the legs (e.g., peripheral arterial disease, arthrosis, spinal disc herniation).
Abbreviation: CVD, chronic venous disease.

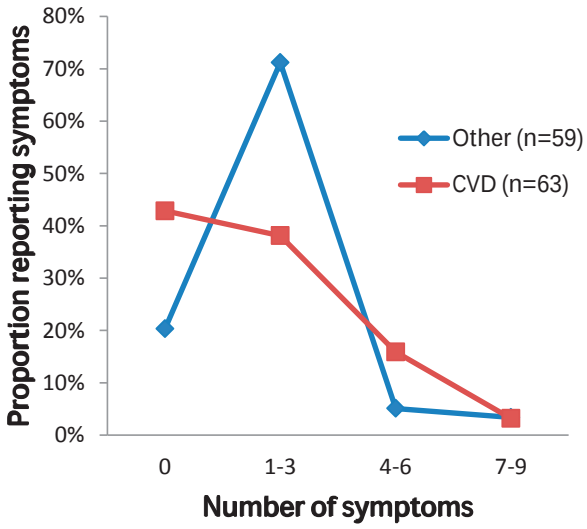

Figure 3. Proportions of patients with a total number of 0, 1-3, 4-6, and 7-9 symptoms according to diagnosis.
Other includes patients with other diseases of the legs (e.g., peripheral arterial disease, arthrosis, and spinal disc herniation)
Abbreviation: CVD, chronic venous disease.

Number of venous symptoms according to diagnosis

Patients were allocated according to the number of reported symptoms (out of a total of nine) into four groups: 0 symptoms, 1-3 symptoms, 4-6 symptoms and 7-9 symptoms. In both the CVD and 'other' group 44% of the patients presented with 4-6 symptoms (Figure 3). In addition, the proportion of patients with 7-9 symptoms in the CVD group was not much higher than in patients affected by other diseases of the leg (29% *vs* 14%).

When we calculated the summary Sym-scores of the 'other' and CVD group, both groups showed similar mean scores (50 *vs* 51). Mean Sym-scores decreased when we compared clinical classes C3-C6 to clinical classes C1-C2 (49 *vs* 50, $p = .32$), indicating a deterioration of symptoms.

Time of the day at which symptoms were experienced most intensely.

Half of the CVD patients experienced their symptoms most intense at the end of the day *vs* 21% in the 'other' group ($p < .001$) (Figure 4). In the 'other' group, 40% of the patients experienced their symptoms at any time of the day.

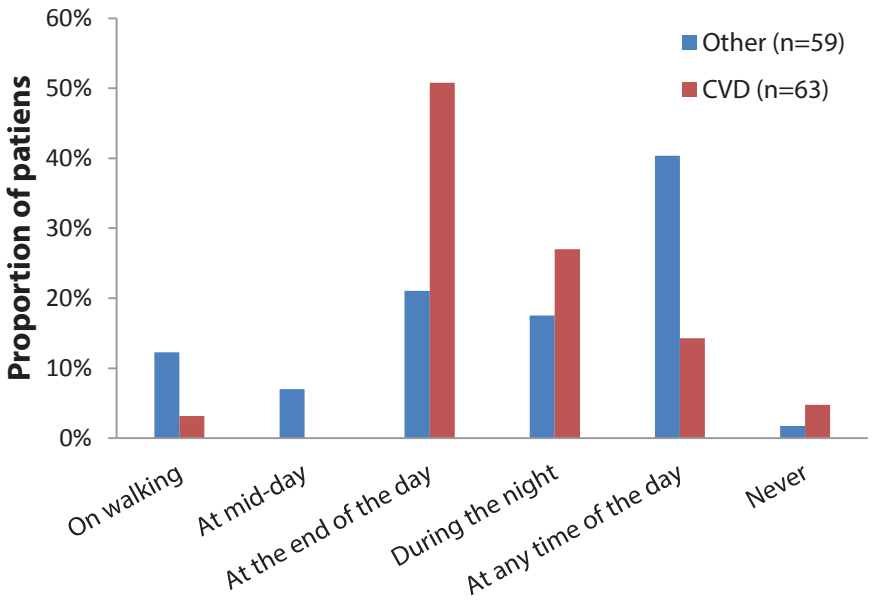

Figure 4. Time of the day at which symptoms were experienced most intense.
Other includes patients with other diseases of the legs (e.g., arthrosis, peripheral arterial disease, spinal disc herniation)
Abbreviation: CVD, chronic venous disease.

DISCUSSION

This study showed that the majority of symptoms that are commonly attributed to CVD (heavy legs, swelling, night cramps, restless legs, throbbing, and itching) are slightly more often reported in patients affected by CVD compared to patients affected with other diseases of the legs. Furthermore, there was no strong correlation between type of symptoms and extent and severity of CVD. When CVD patients with clinical class C3-C6 were compared with patients with other leg diseases, differences were small and statistical significance was only found for the symptoms swelling and itching. The largest difference between the CVD and 'other' group was observed with respect to the timing of symptoms. Patients with CVD are more likely to experience symptoms at the end of the day than patients who have symptoms due to other diseases of the legs.

In the present study the mean VEINES-Sym summary score was comparable to that found in other studies.[11,13] Kahn et al. reported mean Sym-scores of 50.5 in males and 49.8 in females. As Kurz et al. already demonstrated, mean Sym-scores decreased with higher clinical classes, ranging from 52.3 for C1 to 43.1 for C5-C6.[11] However, although mean scores were slightly lower in C3-C6 *vs* C1-C2, a significant decrease in mean Sym-scores with increasing severity could not be confirmed in this study.

The considerable overlap between venous symptoms reported by patients with CVD and by patients with other diseases of the legs confirms lack of specificity of venous symptoms. Marston et al.[14] postulated that none of the venous symptoms are specific to venous disease and multiple etiologies may be confused with CVD. The population based Bonn Vein Study revealed that 62.1% of women and 49.1% of men reported leg symptoms, but only 27.8% of men and 34.1% of women had CVD with clinical class above C2 and only 21.0% had reflux in the superficial venous system.[15,16] The Edinburgh Vein Study also showed that lower limb symptoms are not only caused by venous problems. Venous symptoms such as aching and cramps were reported by 54% and 34%, respectively, in the general population.[3] The San Diego Population study related symptoms to CVD and found that swelling, heaviness and itching were reported twice as much by participants with visible or functional venous disease compared to participants with normal legs. Or other symptoms the contrasts were less strong.[2]

Interestingly, we observed a statistically significant difference between both groups in proportion of patients that experienced their symptoms most intensely at the end of the day. This finding is in line with another study showing that circumstances that elicit or exacerbate symptoms were more characteristic for CVD rather than the number of symptoms or symptom type.[17] Several studies already emphasized the importance of a thorough medical history to evaluate the circumstances that elicit and exacerbate symptoms (the time of the day, relief of symptoms by elevation of the legs) and physical examination in combination with venous ultrasound examination.[14,17,18] However,

available questionnaires do not incorporate questions, which explicitly address such symptom-provoking factors. The reason why we used the VEINES-Sym for this study is that it is the most thorough and comprehensive questionnaire on symptom type and symptom frequency that is currently available. Other questionnaires such as the Chronic Lower Limb Venous Insufficiency, and Aberdeen Varicose Vein Questionnaire rather focus on impairment of Health-Related Quality of Life and clinical class related items and to a lesser extent on symptoms.[19,20] The VEINES-Sym questionnaire includes one question concerning at what time of the day the symptoms are most intense. However, precisely this question is not included for calculation of the mean summary Sym-scores and is only used to provide descriptive information.[12]

The present study has a few limitations. First, the groups of patients with and without CVD are small and therefore the power to detect significant differences is limited. The sample size in this study allowed for detection of absolute differences of 25% or more in proportions of reported symptoms with a power of 90% and two-sided alpha of 5%. We assumed that between- group differences smaller than 25% are not clinically relevant, because in case of high specificity of symptoms we expected much larger differences in proportions with reported symptoms between the groups with and without CVD. Second, we did not include a control group of healthy subjects and therefore we were not able to compare the results of the patients with CVD to the proportion of healthy patients reporting symptoms. Third, presence of venous disease in a small fraction of the groups with other disease may have contributed to lack of contrast in symptom frequency between groups, but do not fully explain the finding of small differences in reported prevalence of symptoms between groups with CVD and other diseases.

In conclusion, the lack of difference in prevalence of reported 'venous' symptoms between CVD patients with confirmed reflux and patients with other diseases of the legs suggest that these symptoms may be less specific for patients with refluxing veins than is usually assumed. This finding implies that venous symptom questionnaires can only be used to quantify the degree of symptoms perceived by patients affected with CVD. The VEINES-QOL/Sym questionnaire is not suitable as a diagnostic or screening tool. The results of this study confirm the importance of a thorough history and physical examination, including specific questions about circumstances that elicit, exacerbate or alleviate symptoms, for the differentiation between patients with and without CVD.

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CHAPTER 3

Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins

van der Velden SK
Biemans AAM
De Maeseneer MGR
Kockaert MA
Cuypers PW
Hollestein LM
Neumann HAM
Nijsten T
van den Bos RR

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ABSTRACT

Background: A variety of techniques exist for the treatment of patients with great saphenous vein (GSV) varicosities. Few data exist on the long-term outcomes of these interventions.

Methods: Patients undergoing conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for GSV varicose veins were followed up for 5 years. Primary outcome was obliteration or absence of the treated GSV segment; secondary outcomes were absence of GSV reflux, change in Chronic Venous Insufficiency quality-of-life Questionnaire (CIVIQ) and EuroQol-5D (EQ-5D™) scores.

Results: A total of 224 legs were included (69 CS, 78 EVLA, 77 UGFS), 86.2% of which were evaluated at final follow-up. At 5 years, Kaplan–Meier estimates of obliteration or absence of the GSV were 85% (95% confidence interval [CI] 75 to 92), 77% (66 to 86) and 23% (14 to 33) in the CS, EVLA and UGFS group respectively. Absence of above-knee GSV reflux was found in 85% (73 to 92), 82% (72 to 90) and 41% (30 to 53) respectively. CIVIQ scores deteriorated over time in patients in the UGFS group (0.98 increase per year, 95% CI 0.16 to 1.79), and were significantly worse than those in the EVLA group (−0.44 decrease per year, 95% CI −1.22 to 0.35) (p = .013). CIVIQ scores for the CS group did not differ from those in EVLA and UGFS groups (0.44 increase per year, 95% CI. −0.41 to 1.29). EQ-5D™ scores improved equally in all groups.

Conclusion: EVLA and CS were more effective than UGFS in obliterating the GSV 5 years after intervention. UGFS was associated with substantial rates of GSV reflux and significantly inferior CIVIQ scores compared with EVLA and CS. Registration number: NCT00529672 (http://www.clinicaltrials.gov).

INTRODUCTION

Many treatment options are available for patients with symptomatic reflux of the great saphenous vein (GSV) or small saphenous vein (SSV). They include endovenous thermal ablation (EVTA) with laser, radiofrequency or steam, ultrasound-guided foam sclerotherapy (UGFS), and conventional surgery (CS). Current guidelines,[1-3] which recommend EVTA as the treatment of choice for a refluxing saphenous vein, are based largely on studies with short- or mid-term follow-up. However, the high recurrence rates of varicose veins emphasize the need for long-term follow-up. Several long-term prospective case series have been published reporting success rates for CS, EVTA and UGFS of up to 94%, 90% and 58% respectively.[4–6] High-quality data are sparse and, to date, the results of only two randomized clinical trials (RCTs) have been published,[7,8] showing similar recurrence rates after CS and endovenous laser ablation (EVLA) of the GSV, with follow-up of 5 years.

The objective of the present study was to compare long-term outcomes of CS, EVLA and UGFS 5 years after the intervention. The 1-year results of this trial have been reported previously.[9]

METHODS

Patients were enrolled in a multicenter non-blinded, randomized, three-arm, parallel-group trial at the Departments of Dermatology and Vascular Surgery of two centers (Erasmus MC, Rotterdam, and Catharina Hospital, Eindhoven, The Netherlands). The trial was approved by the research ethics committee at Erasmus MC (MEC-2005-325). The study design, procedures and 1-year outcomes (primary endpoint) have been reported previously.[9] This cohort includes patients who were followed up for up to 5 years postintervention. Details of the study protocol are available at www.clinicaltrials.gov (registration number NCT00529672).

In brief, consecutive patients presenting between January 2007 and December 2009 with lower-limb venous symptoms, after routine screening by means of medical history, clinical examination (defining the clinical class C of the CEAP [Clinical Etiologic Anatomic Pathophysiologic] classification),[10] and duplex ultrasound imaging, were invited to participate in the trial. Only symptomatic patients with saphenofemoral junction (SFJ) reflux (from either the terminal or preterminal valve) and a refluxing GSV above the knee with a diameter of at least 5 mm (measured mid-thigh) were included. Reflux was defined as retrograde flow during more than 0.5 seconds after calf compression. Bilateral inclusion was allowed and each leg was randomized separately. Exclusion criteria were previous treatment of ipsilateral GSV, post-thrombotic syndrome, agenesis of the deep venous system, vascular malformations, use of anticoagulant treatment, pregnancy, heart fail-

ure, known allergy to local anaesthetics or sclerosing agents, immobility, arterial disease (ankle brachial index of less than 0.6), age under 18 years and inability to provide written informed consent.

Concealment of allocation

Eligible limbs of patients who had given written informed consent were randomized in a 1 : 1 : 1 ratio to receive CS, EVLA or UGFS. Treatments were assigned using blocks with a size of six by an independent research nurse at Erasmus MC. Both participating hospitals offered the three treatment options.

Treatment methods

CS consisted of high ligation at the SFJ and closure of the cribriform fascia, followed by invaginating stripping of the above knee GSV and phlebectomies of varicose tributaries. All CS interventions were performed under spinal or general anaesthesia.

EVLA was performed under local tumescent anaesthesia with a 940-nm diode laser. The refluxing GSV was entered at knee level under ultrasound-guidance, and the tip of the laser fibre was positioned 1–2 cm from the SFJ. A bare-tipped fibre was used in all cases. Tumescent anaesthesia was administered under ultrasound-guidance and the sheath with the laser fibre was pulled back continuously at a rate corresponding to 60 J per cm vein (power setting 10 W). Tributaries were removed by phlebectomies, concomitantly or in a subsequent session.

For UGFS, foam was prepared using the Tessari method with 1 ml of 3% polidocanol and 3 ml air.[11] The refluxing GSV was injected directly at the level of the knee under ultrasound-guidance. The volume of injected foam was determined by the length and diameter of the vein, with a maximum of 10 ml per session. Refluxing tributaries were not treated systematically at the time of UGFS, but only in case of complaints. If considered necessary, UGFS of the GSV was repeated once between 3 months and 1 year after the initial treatment.

At the end of all treatments, a compression bandage was applied. After 48 h, the bandage was replaced by a medical elastic compression stocking (ankle pressure 23–32 mmHg) for 2 weeks during the day.

Fully trained staff surgeons performed CS or EVLA procedures. EVLA was also performed by fully trained dermatologists and by dermatology trainees, who were supervised by fully trained staff dermatologists. UGFS was performed only by fully trained dermatologists and dermatology trainees, supervised by the same dermatologists.

Outcomes and follow-up protocol

Outcomes were evaluated at 3 and 12 months, and yearly thereafter. The primary outcome measure was obliteration or absence of the treated part of the GSV 5 years after

treatment. Duplex ultrasound findings of the treated GSV were categorized as follows: completely open with reflux (category 1); partial or segmental obliteration with reflux (category 2); partial or segmental obliteration with antegrade flow (category 3); total obliteration or absence (category 4).[12] For the primary outcome, only patients in category 4 were considered to have had anatomical treatment success. Follow-up duplex ultrasonography was performed by vascular technologists supervised by experienced vascular surgeons, or by dermatology trainees supervised by experienced dermatologists.

Secondary outcomes included absence of above-knee GSV reflux (categories 3 and 4), disease-specific and generic Health-Related Quality of Life (HRQoL) scores, clinical class C, SFJ reflux, presence of neovascularization at the SFJ, progression of venous disease, and number of additional treatments.

Disease-specific HRQoL scores were measured using the Chronic Venous Insufficiency quality-of-life Questionnaire (CIVIQ),[13] and generic HRQoL scores were measured using EuroQol-5D (EQ-5D™; EuroQol Group, Rotterdam, The Netherlands).[14] The latter consists of two separate summarizing scores: EQ visual analogue scale (EQ VAS) and descriptive system (EQ-5D).

The SFJ was checked for the presence or absence of reflux and for neovascularization on duplex imaging.[12] Neovascularization was defined as the presence of small or larger tortuous veins between the saphenous stump or common femoral vein and superficial veins. Neovascularization was classified into two grades. Grade I was defined as tiny veins with a diameter smaller than 4 mm, limited to the groin area. Grade II (i.e., clinically relevant) was defined as larger tortuous refluxing veins (diameter of at least 4 mm) at the SFJ directly connecting with refluxing tributaries at thigh level, a residual refluxing part of the GSV or anterior accessory saphenous vein (AASV).[15]

New refluxing tributaries of the GSV or AASV above or below the knee, appearing after more than 2 years of follow-up, were considered as progression of venous disease. Reinterventions of the GSV above knee level, and additional treatments of the AASV, GSV below knee level, and tributaries above and below knee level, were recorded in patients' files between 1 year and 5 years of follow-up. In patients with symptoms, reintervention or additional treatment was performed.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Continuous variables were normally distributed and compared by one-way ANOVA. Kaplan–Meier analysis was used to estimate survival free from GSV recanalization (categories 1–3), reflux (categories 1 and 2) or neovascularization

Restricted mean survival time (RMST) ratios were calculated, representing the ratio between the mean survival time during a restricted follow-up period (5 years) of two groups.[16]

Measurements over time were analyzed using a linear mixed-effect model. For each outcome the best fitted model was used (random intercept, random intercept and slope, random intercept and slope and non-linear terms). The main analysis included no co-variables. In the multivariable analysis, age was included as a co-variable.

Patients who had both legs randomized were excluded completely from the HRQoL analyses.

Categorical variables were compared using χ^2 or Fisher's exact test. The Bonferroni test was used to correct for multiple testing. Class C and progression of disease were analyzed using a proportional odds mixed-effect model (random slope with random intercept).

SPSS® version 21.0 software (IBM, Armonk, New York, USA) was used for data analysis. Mixed-effect model analyses were conducted using available software (http://www.r-project.org).

RESULTS

A total of 840 patients with varicose veins attending the trial centers were assessed for eligibility between January 2007 and December 2009. Some 240 legs (223 patients) with primary GSV reflux were randomly allocated to CS, EVLA or UGFS (Figure 1). In total, 86.2% of 224 treated legs (170 patients) were evaluated at 5-year follow-up (median length of follow-up 4.8 years).

Demographic data, class C, GSV diameter, and HRQoL impairment were similar among the three groups (Table 1), but patients undergoing EVLA were slightly younger (50.2 years *versus* 52.5 and 56.4 years in CS and UGFS groups respectively; $p = .048$).

Legs in the EVLA group received a mean(standard deviation [SD]) of 59.2(15.2) J/cm. In the UGFS group, the total mean(SD) volume of injected foam was 4.4(2.1) ml.

Primary outcome

Anatomical treatment success (category 4)

At 5 years after intervention, the treated GSV was completely obliterated or absent in 85% (95% confidence interval [CI] 75 to 92) of legs in the CS group, 77% (66 to 86) in the EVLA group and 23% (14 to 33) in the UGFS group ($p < .001$) (Figure 2). Four patients in the CS group received high ligation or UGFS rather than the planned intervention (Figure 1).

Patients treated with CS or EVLA were four times more likely to have persisting obliteration of the above-knee GSV than patients in the UGFS group at 5 years (UGFS/EVLA RMST ratio: 0.6, 95% CI 0.5 to 0.8; UGFS/CS RMST ratio: 0.6, 0.5 to 0.7).

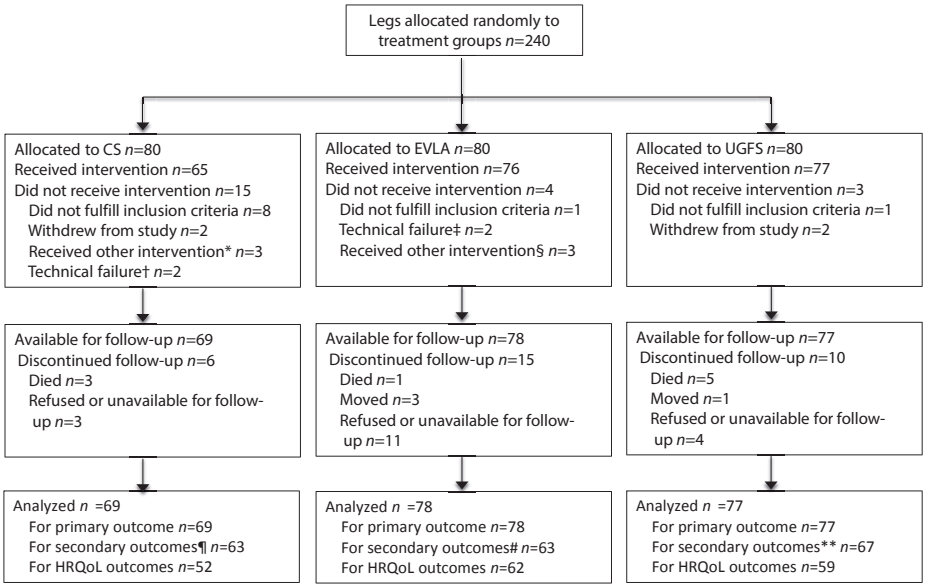


Figure 1. CONSORT diagram for the trial. * One patient was treated with radiofrequency ablation (RFA) and two patients were treated with ultrasound-guided foam sclerotherapy (UGFS); † patients received ligation only; ‡ patients received UGFS instead; § patient received RFA.
For secondary outcomes: presence of saphenofemoral reflux, grades of neovascularization and number of additional treatments were analyzed using the χ^2 test in 63, 63 and 67 limbs in the conventional surgery, endovenous laser ablation (EVLA), and UGFS groups respectively. Absence of great saphenous vein reflux, presence of neovascularization clinical class, progression of disease, number of reinterventions, and additional treatments were analyzed in ¶69, #78 and **77 limbs using Kaplan-Meier and linear mixed effect models. For Health-Related Quality of Life (HRQoL) outcomes, Chronic Venous Insufficiency Quality of life (CIVIQ), EuroQol-5D (EQ-5D™) and visual analogue scale (EQ VAS) scores were analyzed in 52, 62 and 59 patients using linear mixed-effect-models. Patients with bilateral treatment were excluded from HRQoL analysis.

Secondary outcomes

Absence of above-knee GSV reflux (categories 3 and 4)

At 5 years in the CS and EVLA groups, the estimated cumulative proportion of legs without above-knee GSV reflux was 85% (95% CI 73 to 92) and 82% (72 to 90) respectively (Figure 3), compared with 41% (30 to 53) in the UGFS group. Patients treated with CS or EVLA were three times more likely to have absence of above-knee GSV reflux than patients in the UGFS group after 5 years of follow-up (UGFS/EVLA RMST ratio: 0.7, 95% CI 0.6 to 0.8; UGFS/CS RMST ratio: 0.7, 0.6 to 0.8).

Table 1. Baseline characteristics of patients and legs available for follow-up

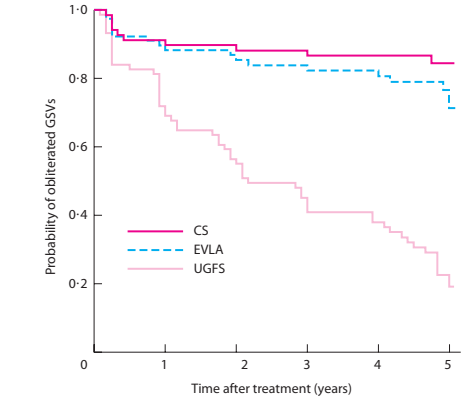
	CS	EVLA	UGFS
Patients	*n*=65	*n*=70	*n*=64
Age (years)*	52.5(15.6)	50.2(14.6)	56.4(13.5)
Sex ratio (F : M)	45 : 20	49 : 21	44 : 20
CIVIQ score*	24.1(19.1)	25.7(21.2)	25.2(19.2)
EQ-5D™*			
Descriptive	0.9(0.1)	0.9(0.2)	0.8(0.2)
EQ VAS	79.0(12.8)	79.5(14.9)	78.7(13.4)
Legs	*n*=69	*n*=78	*n*=77
No. of legs			
Left side	35 (49)	48 (62)	46 (60)
Right side	34 (51)	30 (38)	31 (40)
Unilateral or bilateral treatment			
Unilateral	52 (75)	62 (79)	59 (77)
Bilateral (same treatment for both legs)	8 (12)	6 (8)	10 (13)
Bilateral (other treatment in contralateral leg)	9 (13)	10 (13)	8 (10)
GSV diameter (mm)*	6.2(1.5)	6.4(1.4)	6.1(1)
Clinical class			
C1	1 (1)	0 (0)	1 (1)
C2	32 (46)	37 (47)	34 (44)
C3	21 (30)	29 (37)	30 (39)
C4	14 (20)	8 (10)	8 (10)
C5	1 (1)	0 (0)	1 (1)
C6	0 (0)	0 (0)	0 (0)
Missing	0 (0)	4 (5)	3 (4)

Values in parentheses are percentages unless indicated otherwise; *values are mean (standard deviation). Abbreviations: CS, conventional surgery; EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy; CIVIQ, Chronic Venous Insufficiency quality-of-life Questionnaire; EQ-5D™, EuroQol–5D; VAS, visual analogue scale; GSV, great saphenous vein.

Health-Related Quality of Life scores

Over time, CIVIQ scores were significantly lower - indicating better disease-specific quality of life- in the EVLA than in the UGFS group in the linear mixed-effect model (Figure 4). There were no significant differences between EVLA and CS groups.

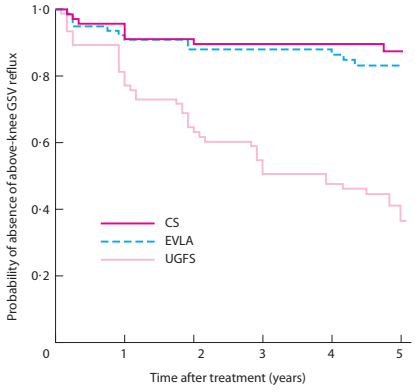
EQ-5D™ scores improved slightly in all three groups over time (Table 2). EQ VAS scores deteriorated in all three groups over time (Supplementary Figure 1). When age was included in multivariable analyses of CIVIQ, EQ-5D™ or EQ VAS scores, no major changes between or within the groups were found when compared with the univariable analysis (data not shown).



No. at risk

CS	69	61	60	57	54	24
EVLA	78	64	60	54	51	29
UGFS	77	52	40	32	26	13

Figure 2. Freedom from recanalization after conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for great saphenous varicose veins.
$p < .001$ (log rank test)



No. at risk

CS	69	64	61	58	55	25
EVLA	78	66	61	57	55	31
UGFS	77	59	46	39	33	18

Figure 3. Freedom from above-knee great saphenous vein (GSV) reflux after conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for great saphenous varicose veins.
$p < .001$ (log rank test)

Table 2. Regression coefficients of CIVIQ and EQ-5D™ scores in the three treatment groups

	CS (*n*=52)	EVLA (*n*=62)	UGFS (*n*=59)
CIVIQ score	0.44 (−0.41, 1.29)	−0.44 (−1.22, 0.35)	0.98 (0.16, 1.79)*
EQ-5D™ score	0.02 (0.01, 0.02)	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)

Values in parentheses are 95 confidence intervals.
*$p = .013$ (endovenous laser ablation [EVLA] *versus* ultrasound-guided foam sclerotherapy [UGFS], linear mixed-effect model). Regression coefficients for the EuroQol visual analogue scale (EQ VAS) model are uninformative because a non-linear model was applied (regression coefficients of natural spline function); Supplementary Figure 1 shows the relation between time after treatment and EQ VAS.
Abbreviations: CS, conventional surgery; CIVIQ, Chronic Venous Insufficiency quality-of-life Questionnaire; EQ-5D™, EuroQol-5D

Clinical class

In the linear mixed-effect model, there was no difference in the distribution of class C between legs treated by CS (odds ratio [OR] 1.4, 95% CI 1.2 to 1.6), EVLA (OR 1.3, 1.1 to 1.5) or UGFS (OR 1.3, 1.1 to 1.5) over time.

Saphenofemoral junction reflux

More legs in the UGFS and EVLA groups had persisting or recurrent reflux at the SFJ than limbs in the CS group at 5 years of follow-up ($p < .001$) (Table 3). No significant differences were observed between EVLA and UGFS ($p = .237$).

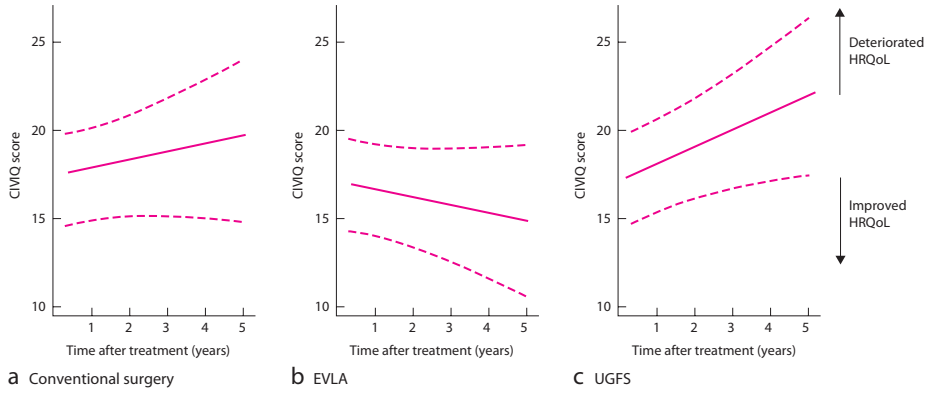


Figure 4. Chronic Venous Insufficiency quality-of-life Questionnaire (CIVIQ) scores with 95% confidence intervals in the 5 years after **a** conventional surgery, **b** endovenous laser ablation (EVLA) and **c** ultrasound-guided foam sclerotherapy (UGFS) for great saphenous varicose veins.
Changes in scores for conventional surgery and EVLA were small and non-significant, whereas those for UGFS were significantly different compared with values in the EVLA group (p = .013, linear mixed-effect model). Table 2 shows regression coefficients for the different CIVIQ scores.
Abbreviation: HRQoL, Health-Related Quality of Life.

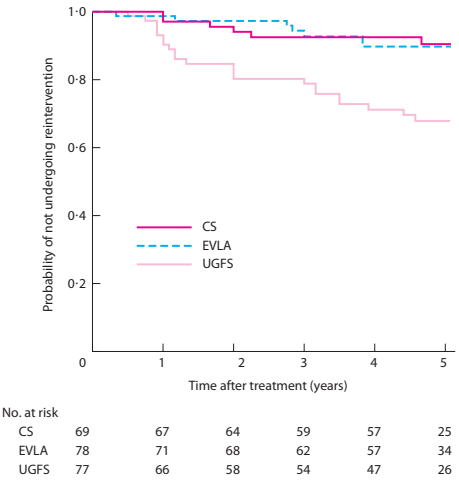


Figure 5. Freedom from reinterventions of above-knee great saphenous vein (GSV) after conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for great saphenous varicose veins.
p < .001 (log rank test)

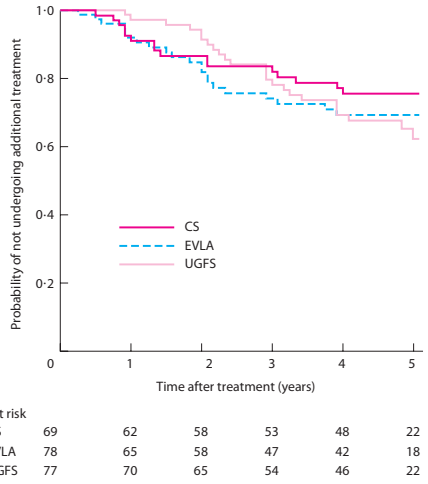


Figure 6. Freedom from additional treatments after conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for great saphenous varicose veins.
p = .546 (log rank test).
Additional treatments included treatments of the anterior accessory saphenous vein, great saphenous vein below-knee level and tributaries above and below-knee level.

Neovascularization

At 5 years, 44% (95% CI 33 to 58) of legs in the CS group, 11% (5 to 20) in the EVLA group and 3% (1 to 9) in the UGFS group had developed some degree of neovascularization (Table 3). Legs treated by CS were more likely to develop neovascularization grade I than those treated by EVLA (OR 12.9, 95% CI 2.8 to 59.2) or UGFS (OR 1.5, 1.2 to 1.8) at 5 years. However, the proportion of patients with grade II neovascularization was similar following CS and EVLA ($p = .606$).

Progression of disease

Progression of disease did not differ between CS (OR 4.2, 3.2 to 5.5), EVLA (OR 4.4, 3.3 to 5.9) and UGFS (OR 4.1, 3.1 to 5.4) groups over time.

Reinterventions and additional treatments

During the 5-year follow-up, 32% of legs treated initially with UGFS required one or more reinterventions of the GSV above the knee (Figure 5). Conversely, only 10% of limbs in the CS and EVLA groups had one or more reinterventions over time. In the UGFS group, GSVs above knee level were more often retreated with UGFS than those in the CS or EVLA group ($p < .001$) (Supplementary Table 1).

Table 3. Distribution of reflux in 193 legs of patients who attended the 5-year follow-up visit

	CS (*n*=63)	EVLA (*n*=63)	UGFS (*n*=67)	*p**
GSV reflux				
Above-knee	8 (13)	11 (17)	35 (52)	< .001†
Below-knee	17 (27)	17 (27)	15 (22)	.412
Missing	9 (14)	14 (22)	19 (28)	
AASV reflux	3 (5)	8 (13)	8 (12)	.133
Missing	10 (16)	17 (27)	17 (25)	
SFJ reflux	8 (13)	14 (22)	21 (31)	.003‡
Missing	0 (0)	6 (10)	1 (1)	
Neovascularization				
Grade I	17 (27)	2 (3)	3 (4)	< .001‡
Grade II	11 (17)	8 (13)	3 (4)	.009§
Refluxing tributaries				
Above-knee	16 (25)	22 (35)	20 (30)	.426
Below-knee	18 (29)	15 (24)	21 (31)	.106

Values in parentheses are percentages. *χ^2 test. † $p < .050$, conventional surgery (CS) and endovenous laser ablation (EVLA) *versus* ultrasound-guided foam sclerotherapy (UGFS); ‡ $p < .050$, EVLA and UGFS *versus* CS; § $p < .050$, CS *versus* UGFS (all χ^2 test).

Abbreviations: GSV, great saphenous vein; AASV, anterior accessory saphenous vein, SFJ, saphenofemoral junction.

The number and types of additional treatments were similar among the three groups (Figure 6), except for UGFS of the GSV below knee level which was performed only in CS and EVLA groups (5% and 11% respectively *versus* 0% in the UGFS group) (Supplementary Table 1).

DISCUSSION

This study has demonstrated that total obliteration or absence of the GSV was more frequent in legs of patients treated with CS or EVLA than in those treated with UGFS after 5 years of follow-up. Above-knee GSV reflux was more frequently present after UGFS. Disease-specific HRQoL outcomes were better in patients treated with EVLA than in those treated with UGFS.

Two RCTs[7,8] have compared the results of CS and EVLA at 5 years' follow-up, showing absence or obliteration of the treated GSV in 90–100% following CS and 82–93% after EVLA. In the present study, the proportion of patients with absence of the GSV after CS (85%) was lower than that reported in other studies with 5 years of follow-up.[4,7,8,17] There are several possible explanations for this discrepancy, such as violation of protocol and randomization, 'blind' stripping and definition of outcome. Four patients with anatomical failure did not receive the allocated CS, but only high ligation or UGFS. However, owing to the intention-to-treat design of the initial RCT, these patients were analyzed in the CS group. Stripping was not guided by ultrasound imaging, and 'blind' stripping of the above-knee GSV may have been incomplete. In a prospective study[18] looking at completeness of stripping related to quality of life, a segment of GSV could be found at duplex ultrasonography after 2 years in more than half of cases. The present authors' definition of treatment success was very strict: if the GSV was present segmentally above knee level, this was considered an anatomical failure (this was the case in four limbs). In the present study, after treatment with EVLA, the anatomical success rate (77%) was comparable to the findings of several long-term prospective studies[5,19,20] that reported GSV obliteration rates of between 75% and 90%, but slightly lower than in previously published RCTs[7,8] with comparable length of follow-up. This difference may again be explained by the difference in definition of treatment success.[7,8] Interestingly, the proportion of patients with GSV reflux during follow-up was similar to that of other RCTs.[7,8] Other possible explanations are the difference in study design (randomized *versus* prospective) and selection bias, because the proportion of patients lost to follow-up in the present study was far lower than in other studies (13.8% (31 of 224) *versus* 21.3%,[5] 36.7%,[7] and 32.9%[8]).

The obliteration rate after UGFS was 20% to 50% lower than in previous mid- and long-term reports of RCTs and prospective cohort studies.[6,21,22] This difference in UGFS

efficacy between studies might be due to factors such as treatment protocol of UGFS, combination therapy (e.g., adding phlebectomies or high ligation) and inclusion of large-diameter GSVs. The GSV was punctured at the level of the knee and a single direct injection was usually performed, possibly decreasing the efficacy of the injected foam at the proximal thigh.[23] Only one retreatment of the GSV was allowed during the first year, whereas other studies allowed more retreatments.[22] In addition, mean volumes of injected foam in the first session were lower than in other studies.[6,21,24,25] However, if UGFS is repeated over time and larger volumes of foam are used, it can be a very effective treatment.[24] In the present study, concomitant phlebectomies of refluxing tributaries were not performed systematically at the time of UGFS of the GSV, in contrast with the previously published four-arm RCT.[21] It can be hypothesized that persisting inflow from tributaries locally reduces the effect of sclerotherapy and hence induces prompt recanalization of an initially formed thrombus in the GSV. Indeed, as albumin neutralizes the sclerosant drug, this neutralizing effect will be more pronounced where the blood volume is larger, which may result in less efficacious damage of endothelial cells at the site of inflow from a tributary.[26] Reflux at the SFJ was not treated, as is conventional for EVTA or UGFS treatment. In a small RCT,[6] however, additional high ligation at the SFJ in UGFS-treated patients resulted in obliteration rates of 58%, compared with 54% in the CS group at 5 years' follow-up. Adding high ligation in the UGFS group may have influenced the final results in this particular study,[6] but more studies are needed to confirm these findings. It should be acknowledged that, if UGFS is combined with high ligation, it can no longer be considered a non-invasive treatment.

Several studies have found that UGFS is less effective in large than in smaller saphenous veins.[24,27] The mean GSV diameter was greater than 6 mm, and this might have resulted in a higher recanalization rate. Nevertheless, UGFS can be a valuable alternative in older patients, when there are contraindications to CS or EVTA, and in patients with small-diameter saphenous veins.[24] UGFS may also be an excellent choice for the treatment of patients with symptomatic recurrent varicose veins, and can easily be used in combination with other techniques.[28,29] Therefore, UGFS should still be considered a valuable treatment option in selected patients with varicose veins.

In the UGFS group disease-specific HRQoL scores deteriorated, whereas the HRQoL in the CS and EVLA group remained stable over time. This deterioration is probably related to the presence of persisting above-knee GSV reflux despite retreatment of the GSV. These limbs were mostly retreated with UGFS, which was a less effective technique than CS or EVLA. One long-term prospective study[30] reported a significant improvement of patients' symptoms, lifestyle and Aberdeen Varicose Vein Symptom Severity scores following UGFS in 285 patients. Retreatment was required in only 15% of limbs during 5-year follow-up, compared with 32% of legs in the present study. However, there might have been some bias in their results, as it was a non-randomized study.

The difference in HRQoL and VAS scores between groups could have been influenced by age, as patients undergoing EVLA were younger than those having UGFS or CS. However, adjustment for age in the HRQoL analysis resulted in similar results when compared to the univariable analysis. SFJ reflux was present more frequently following UGFS and EVLA than after CS. In another study,[31] comparing EVLA *versus* CS performed with local tumescent anesthesia, duplex-detected saphenofemoral reflux was also significantly more frequent 2 years after EVLA than after CS (18% *versus* 1% respectively). Apart from the use of a special technique invaginating the GSV stump after high ligation, the fact that these operations were performed using local tumescent anesthesia may also have reduced operative trauma, and hence minimized the risk of developing neovascularization. Interestingly, although duplex ultrasonography-detected grade I neovascularization was observed more frequently in the CS group than in the other two groups, the proportion of limbs with clinically relevant neovascularization grade II was similar between the CS and EVLA group (17% *versus* 13% respectively). In addition, progression of disease was similar in the three groups. These observations suggest that the extent of disease progression is independent of venous treatment.[5,14,24]

The comparable clinical evolution and progression of the disease in the three treatment groups is consistent with previous findings.[7,8,32] Rasmussen and colleagues[21] reported the 3-year follow-up of a RCT comparing four different GSV treatments (e.g., CS with local tumescent anesthesia, EVLA, radiofrequency ablation and UGFS, all with concomitant phlebectomies) and observed no differences between the four groups in Venous Clinical Severity Score and quality of life; nor was there a difference in the incidence and anatomical location of recurrent tributaries. Recently, a RCT[32] comparing CS, EVLA with high ligation, and EVLA without high ligation confirmed that clinical recurrence did not differ between the three treatment groups up to 6 years after treatment. It is clear that, irrespective of the technique employed to treat varicose veins, progression of disease cannot be stopped in the long-term. Genetic predisposition and other patient-related factors (such as body mass index of 30 kg/m^2 or above, pregnancy after the intervention) certainly play a role.[33,34] After several years, tortuous neovascular veins or (newly) refluxing veins at the SFJ may connect with the AASV or superficial refluxing tributaries of the thigh or leg, resulting in clinically obvious recurrent varicose veins.[35]

This study has several limitations. First, blinding of physicians, patients and outcome assessors was not possible owing to the nature of the interventions. Second, patients in the EVLA group were significantly younger than those in the other two groups, although probably due to chance. Third, HRQoL analysis was possible only in patients with unilateral inclusion. Fourth, 13.8% of patients (31 limbs) were lost to follow-up at 5 years because the patient had discontinued, died or moved. However, this value is lower than that reported in similar studies.[7,8]

This study suggests that CS and EVLA are more effective than UGFS in the treatment of GSV reflux. EVLA provides better disease-specific patient-reported outcomes than UGFS after 5 years of follow-up. Thus, CS and EVLA can both be considered efficient treatments with long-term beneficial effects in patients with GSV reflux.

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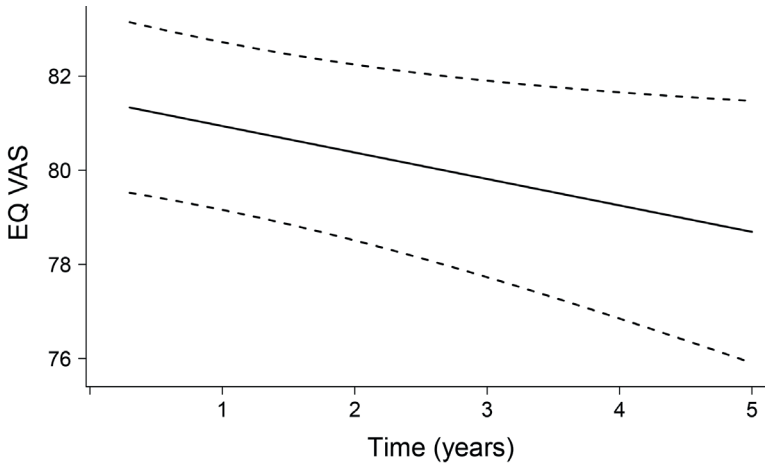
SUPPLEMENTARY

Supplementary Table 1. Reinterventions and additional treatments

	CS (*n*=63)	EVLA (*n*=63)	UGFS (*n*=67)	*p**
Reinterventions of above-knee GSV, No. (%)				
UGFS	5 (8)	5 (8)	23 (34)	< .001†‡
EVLA	2 (3)	1 (2)	3 (5)	.703
RFA	0 (0)	1 (2)	0 (0)	1.000
Stripping	1 (2)	1 (2)	0 (0)	.774
High ligation	0 (0)	2 (3)	0 (0)	.330
Additional treatments				
Above-knee AP	4 (6)	8 (13)	13 (19)	.070
Below-knee AP	9 (14)	4 (6)	10 (15)	.214
UGFS of tributaries				
Above knee	2 (3)	3 (5)	1 (1)	.703
Below knee	6 (10)	5 (6)	3 (4)	.544
UGFS of below-knee GSV	3 (5)	7 (11)	0 (0)	.015§
UGFS of AASV	1 (2)	0 (0)	1 (1)	.744
Unknown	5 (8)	13 (21)	12 (18)	.216

Values in parentheses are percentages.
* Fisher's exact test, except † χ^2 test. ‡ $p < .050$, conventional surgery (CS) and endovenous laser ablation (EVLA) *versus* ultrasound-guided foam sclerotherapy (UGFS); § $p < 0.050$, EVLA *versus* UGFS (χ^2 test).
Abbreviations: GSV, great saphenous vein; RFA, radiofrequency ablation; AP, ambulatory phlebectomies; AASV, anterior accessory saphenous vein.



Supplementary Figure 1. EuroQol visual analogue scale (EQ VAS) scores in the 5 years after conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for great saphenous varicose veins (all groups combined)

CHAPTER 4.1

Postural diameter change of the saphenous trunk in chronic venous disease

van der Velden SK
De Maeseneer MGR
Pichot O
Nijsten T
van den Bos RR

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ABSTRACT

Objective: The aim of this study was to analyze the correlation between the extent of diameter change from standing to supine position, ('postural diameter change', PDC), and patient or duplex ultrasound (DUS) characteristics in lower limbs with and without saphenous trunk (ST) reflux.

Methods: Measurements were carried out in 193 limbs with primary great saphenous vein, anterior accessory saphenous vein or small saphenous vein reflux and 48 control limbs without ST reflux. The inner diameter of the ST was measured with DUS in standing and lying positions. The PDC, calculated as a percentage, followed the formula: (standing diameter - lying diameter)/standing diameter x 100. Clinical findings (according to the highest 'C'- of the CEAP classification), Venous Clinical Severity Score, body mass index (BMI), time of visit, inside and outside temperature were documented. Limbs were divided into two groups using the median value of PDC as a cut-off to increase interpretability of the analysis.

Results: The median PDC was 19% in limbs with ST reflux compared with 24% in control limbs (p = .16). In limbs with and without ST reflux, only older age and increased BMI were independently associated with a low PDC of the ST (R^2 0.13). In limbs with ST reflux, median PDC was significantly lower in C4-C6 (16%, interquartile range [IQR] 8 to 21) than in C0-C1 (23%, IQR 12 to 35) or C2-C3 limbs (21%, IQR 11 to 33) (p = .016). In addition, PDC was significantly lower in veins with a large diameter (>7 mm) than in those with a small diameter (p = .003).

Conclusion: Low PDC of the ST correlates with older age and increased BMI. Whether PDC might become a useful additional DUS tool to classify the severity of chronic venous disease and thereby influence the management strategy should be further investigated.

INTRODUCTION

The wall of the saphenous trunk (ST) and tributaries plays a pivotal role in the development of chronic venous disease (CVD). In patients with CVD, several pathophysiological mechanisms contribute to the inflammation and subsequent remodeling of the venous wall and valves.[1] Histological studies of varicose veins have revealed hypertrophy of the vein wall with increased collagen content, hypertrophic smooth-muscle cells and fragmentation of elastin fibers with degradation and accumulation of extracellular matrix.[2-6] Smooth muscle cells in the venous wall have a disturbed collagen synthesis, resulting in overproduction of rigidity-mediating collagen type I and reduced synthesis of distensible collagen type III. This disturbed ratio contributes to the lack of elasticity of varicose veins.[6,7]

When a healthy individual changes from standing to supine position venous hydrostatic pressure in the lower limbs drops and diameters of the STs decrease. In lower limbs with CVD and ST reflux it could be expected that, in view of the reduced elasticity of the vein wall, diameter decrease will be less significant than in healthy limbs. It can also be hypothesized that this decrease will be lower in limbs with more advanced CVD than in limbs with C2 according to the CEAP classification[8] or in the limbs of healthy individuals. This is supported by the finding that limbs with C4-C6 have less elastic tissue in the venous wall of the great saphenous vein (GSV) than those with C2 or healthy controls.[9] Possibly, the extent of diameter change between standing and supine position, measured by duplex ultrasound (DUS), further described as 'postural diameter change' (PDC) is a reflection of the severity of venous remodeling and hence could be useful in classifying the severity of CVD.

The objective of the present cross-sectional study was to investigate the PDC in limbs with and without ST reflux. The second objective was to analyze patient and DUS findings associated with this PDC.

METHODS

Patients were enrolled in a two-center prospective cross-sectional study at the Department of Dermatology (Erasmus MC, Rotterdam, The Netherlands) and in a private practice (Centre de Médecine Vasculaire, Grenoble, France). The research ethics committee at Erasmus MC approved the trial (MEC-2014-035). Lower limbs of all consecutive patients with primary GSV, anterior accessory saphenous vein (AASV) or small saphenous vein (SSV) reflux were screened for eligibility to be included in the study between March 2014 and May 2015. Reflux in the ST was defined as retrograde flow >0.5 seconds after calf compression-release. Exclusion criteria were previous treatment of ipsilateral GSV, AASV, SSV or tributaries, acute deep or superficial vein thrombosis, previous superficial

vein thrombosis, congenital vascular malformation, post-thrombotic syndrome (obstruction and reflux type), pregnancy or inability to stand. Only one ST of each limb with reflux was included. In addition, a control group of limbs without reflux was established, consisting of contralateral limbs or a randomly chosen limb of other patients all without varicose veins (C0 or C1) or limbs of volunteers without varicose veins working at the Department of Dermatology of Erasmus MC.

In patients and volunteers who had given informed consent, clinical findings (according to the highest 'C'-class) and Venous Clinical Severity Score (VCSS)[10] of examined limbs were documented, as well as age, gender, body mass index (BMI), time of visit, temperature of the examination room (in degrees Celsius) and outside temperature. DUS scanning (CX50, transducer L12-3 and iU22, transducer L12-5, Philips, Bothell, US) was performed either by a dermatology trainee (SvdV at Erasmus MC), working in a supervised setting, or an experienced angiologist (OP in Grenoble). A standard protocol as described in two consensus documents of the International Union of Phlebology (UIP) was followed.[11,12] The STs were first examined in standing position. Manual calf compression-release was used in addition to Valsalva maneuver to assess antegrade flow or reflux. The GSV above knee level and the SSV in the calf were divided into three equal segments (proximal third, mid third and distal third) to determine the extent of ST reflux (Figure 1). The deep venous system was checked for the absence of obstruction and/or reflux. First, in the standing position, compressibility of the common femoral vein (CFV), popliteal vein and calf veins was tested, and the femoral as well as the popliteal veins were checked for the absence of deep venous reflux. If no obvious phasic flow pattern was present in the CFV, additional DUS of the pelvic veins was performed in supine position, to exclude any iliac obstruction.

Measurement of ST diameter

For the present study the inner diameters were measured (from intima to intima), holding the probe transversely (for STs) or longitudinally (for the measurement 3 cm below the saphenofemoral junction [SFJ]) without exerting any pressure. To determine exactly the distance of 3 cm from the SFJ, a longitudinal position of the transducer was needed. Therefore, the diameter at this point also was determined longitudinally by slightly moving the transducer laterally back and forth to measure the largest diameter at 3 cm from the SFJ. Round-shaped veins were measured anteroposteriorly, whereas oval-shaped veins were measured at their largest diameter. When there was a duplication of the SSV, the refluxing and largest SSV was included in the study. If tributaries, focal dilatations or aneurysms were present at the site of the intended measurement, truncal diameter was measured slightly more cranially. A focal dilatation was defined as a local diameter 1.5 to 3 times the diameter of the ST above or below.[13] All measurements were recorded on video (S-VHS).

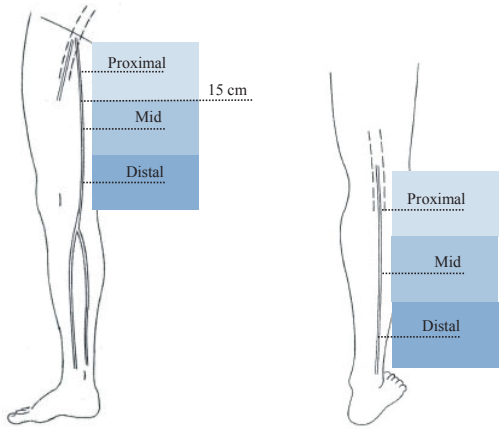

Figure 1. Measurement sites of the great saphenous vein (A) and small saphenous vein (B)

Pilot study to determine the optimal site for diameter measurement

Diameters of the GSV and SSV were measured in 130 limbs with either GSV (*n*=103) or SSV (*n*=27) reflux in at least one segment (proximal, mid or distal third). The diameter of the GSV was measured at five different sites: 3 cm and 15 cm[14] below the SFJ and at the midpoint of the proximal, mid, and distal third segment of the thigh (Figure 1A). In limbs with SSV reflux, its diameter was measured at three sites, respectively, the midpoint of the proximal, mid, and distal third segment of the calf (Figure 1B).

The AASV was not included in the pilot study because this vein is usually relatively short and it is often only measurable close to the SFJ. Therefore, it was decided to use a unique diameter measurement at 3 cm from the SFJ for evaluation of the PDC of the AASV.[12]

The mean diameter of the GSV or SSV of the pilot group was calculated. For the GSV the average of five GSV measurements was taken. To calculate the mean SSV diameter, the average of three SSV measurements was used. The diameter measurement at each site was checked for the smallest difference with the mean, for which an agreement analysis was used. The site with the highest overall agreement was considered as the most representative and was therefore used as the reference site for diameter measurement to evaluate the PDC. For the GSV the reference site was situated at 15 cm from the SFJ and for the SSV at mid-calf (calculations not shown). The latter findings were independent of whether only refluxing segments (no segments without reflux of hypoplastic segments) were included, or all segments.

Postural diameter change of saphenous trunks

In total 241 limbs were included in the study, consisting of 130 limbs of the pilot group, all with either GSV or SSV reflux, 63 additional limbs with GSV, AASV or SSV reflux and 48 limbs of the control group. Based on the findings of the pilot study described above, diameters of the GSV, AASV or SSV were measured in both standing and supine (or prone) position at respectively 15 cm from the SFJ, 3 cm from the SFJ or mid-calf.

First, all measurements were performed with the patients standing. In each included limb the diameter measurement site was marked on the skin to measure exactly at the same site after changing position. Subsequently, the subject was instructed to lie down and, after having remained supine for at least 1 minute, diameter measurement was repeated at the marked site. Measurement of the SSV was performed in the prone position, with the knee slightly bent.

The formula used for calculating the PDC was:

$$\text{postural diameter change (\%)} = \frac{\text{diameter in mm standing - diameter in mm lying}}{\text{diameter in mm standing}} \times 100$$

Inter-observer agreement (reproducibility)

The inter-observer agreement of the diameter measurements was evaluated between the dermatology trainee (SvdV) and the supervising vascular surgeon (MDM). Each repeated the other's measurements at two sites along the GSV (3 cm below the SFJ and at mid-thigh) in ten patients with GSV reflux.

Statistical analysis

Refluxing and control limbs were divided into two groups using the median value of PDC as a cut-off to increase interpretability of the univariable and multivariable logistic regression analysis. Univariable and multivariable (with backward stepwise selection) logistic regression analyzed the association between less than median PDC and limb characteristics in STs with and without reflux. Variables included age, gender, BMI, clinical class, VCSS, reflux of the ST, median diameter of the ST, reflux or no reflux of the junction, and focal dilatations of the ST. Bilaterally included limbs were assumed to be different regarding duplex anatomy and hemodynamics and were therefore considered to be independent observations. Nagelkerke R was calculated to evaluate the goodness of fit of the logistic regression model.

Subsequently, refluxing STs were categorized by clinical class 'C' (distinguishing between C0-C1, C2-C3 and C4-C6) and diameter of the ST (distinguishing between <5 mm, 5-7 mm and >7 mm) to assess the PDC in these different subcategories. Limb characteristics and the influence of the latter on PDC were further evaluated in limbs with ST reflux, subdivided into respectively, those with more and those with less than

median PDC. In the sensitivity analysis of the PDC, the 25th and 75th percentiles of PDC were used as cut-off.

Dichotomous variables were compared using Fisher's exact or χ^2 tests; normally distributed continuous variables were compared using Student t-test and one-way ANOVA. The Mann-Whitney *U*-test was used to compare non-normally continuous variables. The false discovery rate was used to correct for multiple testing.

The inter-observer agreement was calculated by the intraclass correlation coefficient (ICC) using the consistency two-way mixed model. ICC <0.4 reflected a poor reproducibility, between 0.4 and 0.75 a good reproducibility and >0.75 an excellent reproducibility.[14]

All analyses were performed using SPSS® version 21.0 (IBM, Armonk, New York, USA). Two sided *p*-values were considered significant if < .05.

RESULTS

Postural diameter change of refluxing and control saphenous trunks

The PDC of STs was evaluated in 241 limbs of 197 individuals, consisting of 193 limbs with ST reflux and 48 limbs without ST reflux (controls).

The mean ST diameter was 5 mm (interquartile range [IQR] 4 to 6) in the ST reflux group compared with 3 mm (IQR 2 to 6) in the control group. In the group with ST reflux, the median PDC was lower (19%, IQR 11 to 32) than in the control group (24%, IQR 13 to 40) but this difference was not significant ($p = .16$) (Figure 2). Only 10% of the STs in the group with ST reflux showed a PDC of 0% or below, which means the diameter did not change at all or even appeared to become slightly larger. The latter might have been

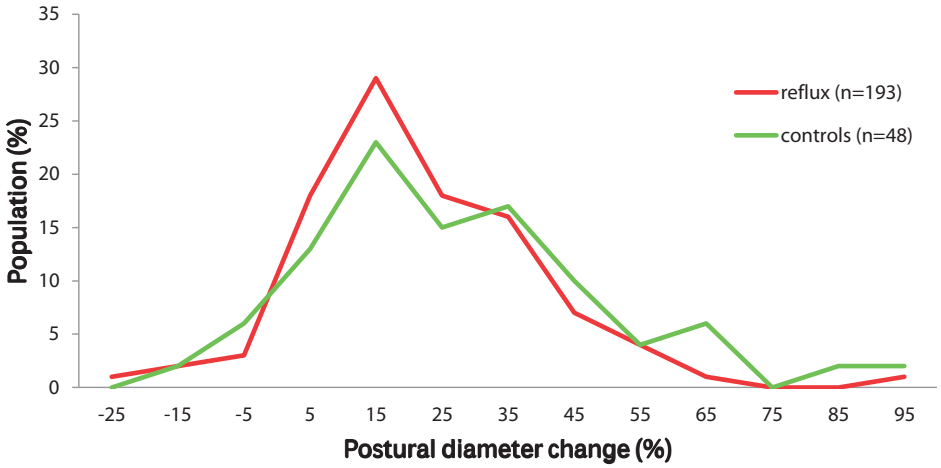

Figure 2. Postural diameter change in refluxing and control saphenous trunks

caused by a measurement error. Limb characteristics of this subgroup with ≤0% change did not differ from the total study population with ST reflux (data not shown).

Predictors of postural diameter change in refluxing and control saphenous trunks

In the univariable analysis, of the nine included variables, age, BMI and median VCSS were significantly associated with an increased risk of a less than median PDC (≤19%) (Table 1).

In the multivariable logistic regression, only age and BMI were associated with less than median PDC (Table 1) resulting in a R^2 of 0.13. Limbs of patients aged >65 years

Table 1. Univariable and multivariable logistic regression of variables associated with ≤ median postural diameter change

	Refluxing and control legs (*n*=241)			
	Univariable OR	**95% CI**	**Multivariable OR**	**95% CI**
Leg				
Control	1.0	-	-	-
Reflux	1.3	0.7, 2.4	-	-
Age in years				
<50	1.0	-	1.0	-
50-65	2.3	1.2, 4.4	1.9	1.0, 3.6
>65	3.9	2.0, 7.6	3.4	1.7, 6.9
Gender				
Females	1.0	-	-	-
Males	1.4	0.8, 2.4	-	-
BMI in kg/m^2				
18-25	1.0	-	1.0	-
25-30	2.6	1.4, 4.8	2.1	1.1, 3.9
>30	2.6	1.4, 5.0	2.6	1.3, 5.1
Clinical class				
C0-C1	1.0	-	-	-
C2-C3	1.2	0.7, 2.2	-	-
C4-C6	2.7	1.2, 6.2	-	-
Median VCSS (IQR)	1.1	1.1, 1.2	-	-
Junction reflux				
Yes	1.0	-	-	-
No	0.7	0.4, 1.2	-	-
Median diameter (IQR) in mm	1.0	0.9, 1.2	-	-
Focal dilatations				
0	1.0	-	-	-
≥1	1.0	0.6, 1.8	-	-

Median was 19% postural diameter change. Nagelkerke R^2 of leg model = .13
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; VCSS, venous clinical severity score; IQR, interquartile range.

were three times more likely to have a less than median PDC compared with those of patients under the age of 50. In addition, the odds for less than median PDC were higher for limbs of obese patients than for those with a normal weight.

Postural diameter change of refluxing saphenous trunks divided by subgroups

The median PDC was significantly lower in C4-C6 (16%, IQR 8 to 21) than in C0-C1 (23%, IQR 12 to 35) or C2-C3 limbs (21%, IQR 11 to 33) ($p = .016$) (Figure 3). If the PDC was classified by diameter of the ST, a similar trend was observed, with a significantly lower PDC in large diameter veins than in small diameter veins ($p = .003$; Figure 4). The diameter of

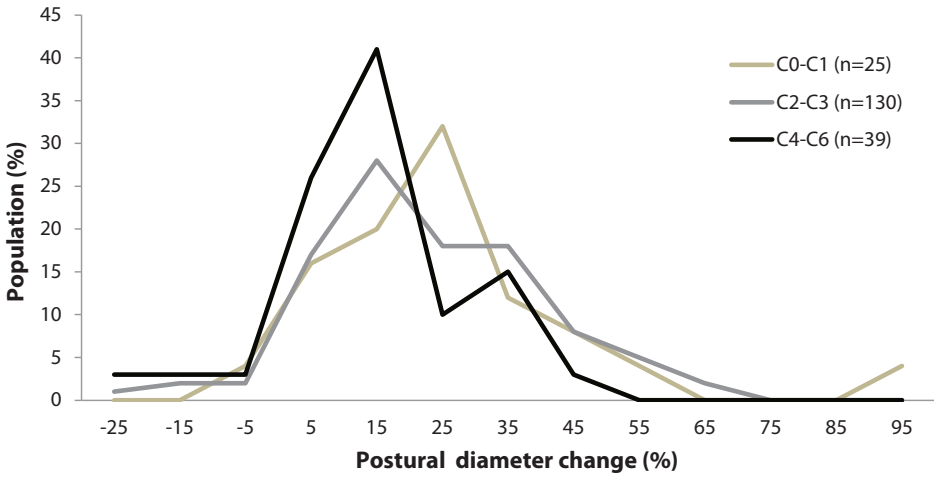

Figure 3. Postural diameter change in refluxing saphenous trunks classified by clinical class

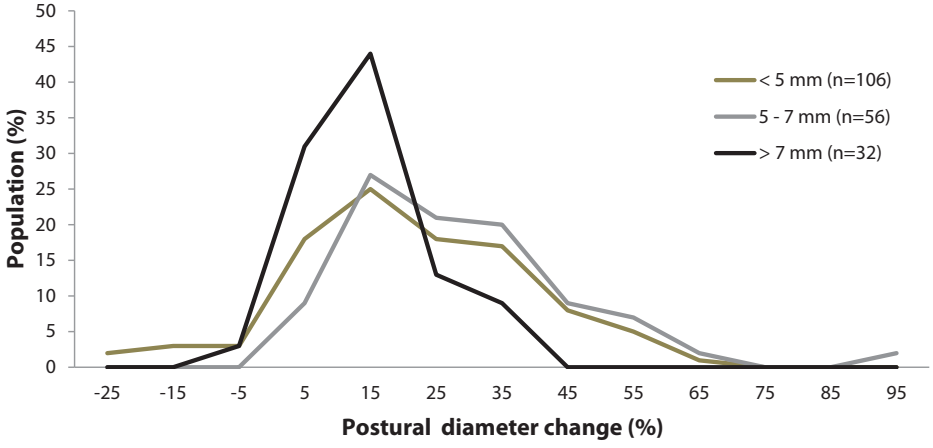

Figure 4. Postural diameter change in refluxing saphenous trunks classified by diameter of the saphenous trunk

the ST dropped to below 4 mm in supine position in 76% of C0-C1 limbs, in 62% of C2-C3 limbs and in only 31% of C4-C6 limbs.

When limbs with ST reflux were subdivided into two groups, those with more and those with less than median PDC, 96 limbs had ≤19% and 97 limbs had more than 19% PDC. Distribution of demographic data of the patients, as well as clinical class, VCSS and DUS data of the affected limbs in these two groups was similar, except that limbs belonging to the group with ≤19% were limbs of older patients (p = .003) and more often of obese patients (BMI >30 kg/m^2; p = .002) (Table 2). However, the p-value for BMI was no longer significant after correction for multiple testing.

Table 2. Discriminative overview between refluxing legs with ≤ median postural diameter change, refluxing legs with > median postural diameter change and controls.

	≤ median (19%) (*n*=96)	**> median (19%) (*n*=97)**	***p*-value***	**Controls (*n*=48)**
Age, No. (%) in years			.003	
<50	21 (22)	42 (45)		14 (29)
50-65	33 (34)	31 (32)		24 (50)
>65	42 (44)	25 (25)		10 (21)
Gender, No. (%)			.270	
Females	64 (67)	73 (75)		36 (75)
Males	32 (33)	24 (25)		12 (25)
Side, No. (%)			.943	
Left	48 (50)	48 (50)		22 (46)
Right	48 (50)	49 (50)		26 (54)
Saphenous vein, No. (%)			.981	
GSV	71 (74)	71 (73)		41 (85)
AASV	11 (15)	12 (12)		2 (4)
SSV	14 (11)	14 (14)		5 (11)
BMI, No. (%) in kg/m2			.005†	
18-25	29 (30)	54 (56)		25 (50)
25-30	37 (39)	26 (27)		10 (21)
>30	30 (31)	17 (18)		14 (29)
Median height (IQR) in cm	171 (163, 178)	172 (165, 178)	.134	171 (166, 176)
Median weight (IQR) in kg	80 (70, 98)	74 (63, 85)	.005†	73 (66,84)
Clinical class, No. (%)			.051	
C0-C1	10 (10)	15 (16)		48 (100)
C2-C3	60 (63)	69 (71)		
C4-C6	26 (27)	13 (13)		
Median VCSS (IQR)	5 (3, 7)	4 (3, 6)	.300	1 (1,2)
Median diameter (IQR) in mm	5 (3, 7)	5 (4, 6)	.880	3 (2, 6)
Varicose veins, No. (%)				
Thigh	39 (41)	28 (29)	.086	0

Table 2. (continued)

	≤ median (19%) (*n*=96)	> median (19%) (*n*=97)	*p*-value*	Controls (*n*=48)
Calf	42 (44)	43 (44)	.602	0
Junction reflux			.455	
Yes	66 (69)	59 (61)		0
No	26 (27)	34 (35)		48 (100)
Other	4 (4)	4 (4)		0
Median temp inside (IQR) in °	21 (21, 23)	21 (21, 23)	.373	21 (20, 21)
Median temp outside (IQR) in °	15 (9, 20)	15 (11, 19)	.773	15 (11, 18)
Median time visit (IQR) in hr	1130 (1019, 1386)	1100 (942 1400)	.397	1260 (947, 1487)
Focal dilatations, No. (%)			.920	
0	64 (67)	64 (66)		48 (100)
≥1	32 (33)	33 (34)		
Refluxing segments, No. (%)				
Proximal	91 (95)	89 (92)	.400	0
Mid	75 (78)	80 (83)	.447	0
Distal	69 (72)	72 (74)	.713	0

* Mann-Whitney *U*-test (height, weight, venous clinical severity score (VCSS), diameter, temp inside, temperature (temp) outside, time visit) or χ^2 (age, gender, site, saphenous vein, body mass index (BMI), clinical class, varicose veins, junction reflux, focal dilatations, refluxing segments).

† *p*-value was non-significant after false discovery rate control.

Abbreviations: GSV, great saphenous vein; AASV, anterior accessory saphenous vein; SSV, small saphenous vein; IQR, interquartile range; hr, hours.

In the sensitivity analysis of the <25th percentile (<11%) *versus* the >75th percentile (≥32%), distribution of patients' and limbs' characteristics remained similar between the two groups (Supplementary Table 1). In addition, similar independent variables were found in the multivariable logistic regression analysis except for the VCSS (Supplementary Table 2).

Inter-observer agreement (reproducibility)

The ICC was excellent for diameter measurement at 3 cm below the SFJ (0.93, 95% confidence interval [CI] 0.73 to 0.98) and at mid-thigh (0.96, 95% CI 0.87 to 0.99).

DISCUSSION

First, this study shows that the ST diameter measured in the standing position, decreased in the lying position in 90% of limbs with ST reflux. The median ST diameter decrease was 19% in patients with ST reflux compared with 24% in controls without ST reflux.

Second, despite clinical class and diameter of the ST tending to influence PDC, only age and BMI were independently associated with a low PDC of the ST.

In 90% of limbs with ST reflux, the diameter of the vein reduced in lying position compared with the diameter measured in the standing position. This seems to confirm that, despite the known remodeling of the venous wall in limbs with varicose veins and chronic venous insufficiency,[16] the vein wall of refluxing STs may still have sufficient elastic properties to adapt to reduced hydrostatic pressure. Other circumstances in which STs of limbs with CVD show significant elasticity have been described. In a small prospective study in pregnant women with varicose veins, the diameters of refluxing GSVs decreased significantly between the third trimester and postpartum period.[17] Equally, certain treatment strategies may induce a reduction in GSV diameter. A significant reduction of GSV diameter was found following isolated phlebectomies (so called 'ASVAL' procedure, ambulatory selective varices ablation under local anesthesia) in C2-C4 limbs with GSV and tributary reflux.[18,19]

The median PDC was found to be slightly higher in control STs than in refluxing STs. The PDC of the vein might be associated with the characteristics of proteins of the extracellular matrix in the venous wall.[6] Comparison of biophysical properties between varicose and control veins showed loss of elastin in the adventitia and selective reduction of type III collagen in the intima of varicose veins.[6,7]

PDC was not influenced by presence or absence of junction reflux. Although this may appear surprising, at a less advanced stage of the disease, the quality of the vein wall, in particular its elasticity, may still be good, even if there is already reflux at the junction. In such cases PDC may still be high because of good elasticity of the vein wall. Only in longstanding disease does the ST become dilated with deterioration of the quality of the vein wall, reflected by a lower PDC. This means PDC is independent of the presence or absence of reflux at the junction, but rather reflects the quality of the vein wall.

Age and BMI were independently associated with reduced PDC. Decreased PDC of the ST in the elderly was confirmed in a small prospective study comparing healthy elderly males (mean age 70 years) with healthy young males (mean age 25 years).[20] In healthy veins elastic properties of the ST seem to diminish with increasing age, and this is probably part of the normal aging process. The decreased PDC in older patients might also be explained by the correlation between age and clinical class. Labropoulos et al.[21] showed previously that patients with skin changes are significantly older than patients with C1-C3 disease. This is obvious as the disease duration is usually longer and the prevalence of previous thrombosis and the presence of deep venous reflux is higher in patients with skin damage. However in the present study patients with deep vein thrombosis were excluded from analysis, and it appeared that only age and BMI were independent factors in the multivariable analysis. In obese patients, decreased PDC

might be explained by the relative obstruction of venous return and increased venous filling pressures, in both the standing and supine positions.[15,22]

Previous studies have shown that ST diameter is correlated with C class and with the source of reflux.[23,24] Although a trend towards lower PDC was observed with increasing C class as well as with increasing diameter of the ST, neither variable was included in the final multivariable model. This might have been influenced by the small number of limbs with C4-C6 and large diameter veins in the present study. Future histological studies should focus on the biophysical properties of varicose veins and their association with PDC.

Understanding the correlation between PDC and elastic properties of the ST may eventually help to determine management strategies in patients with CVD. For example, a high PDC of the vein might point to the presence of relatively high elasticity of the vein wall, for which a less invasive strategy (e.g., ASVAL) might be preferred. In patients with an obvious multifocal or ascending origin of of ST reflux (i.e., reflux starting at the level of the tributaries and progressing towards the ST and eventually to the junction)[25] and a large refluxing tributary, treatment with ASVAL may be a good option.[26] In these patients, a high PDC of the refluxing ST at baseline might predict a higher change of successful treatment (including restoration of ST competence), after ASVAL than a low PDC. However, the value of PDC for clinical practice requires further investigation.

This study has some potential limitations. First, limbs of patients with contralateral varicose veins have been included and therefore genetic predisposition may have influenced PDC. Second, higher clinical class may have been underpowered because the study population had predominantly less advanced stages of CVD (C2 or C3). Third, venous diameters may be subject to change during the menstrual cycle[27] and in the course of the day or season (changing temperature). However, no exogenous factors such as time of visit, inside and outside temperature were found to influence the PDC of the ST (Table 2). Fourth, the PDC was ≤0% in 10% of the refluxing STs, which may suggest an error in measurement.

CONCLUSION

In conclusion, the present study shows that in most limbs with ST reflux, the ST diameter reduces in supine position, with a median decrease of 19%. Low PDC of the ST correlates with older age and increased BMI. Whether PDC can become a useful additional tool in determining treatment strategies in patients with varicose veins and chronic venous insufficiency should be further investigated.

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SUPPLEMENTARY

Supplementary Table 1. Discriminative overview between refluxing legs <25th percentile postural diameter change, legs with ≥75th percentile postural diameter change

	<25th percentile (*n*=49)	**≥75th percentile (*n*=48)**	***p*-value***
Age, No. (%) in years			.001†
<50	14 (29)	31 (65)	
50- 65	13 (26)	10 (21)	
>65	22 (45)	7 (14)	
Gender, No. (%)			.059
Females	29 (59)	37 (77)	
Males	20 (41)	11 (23)	
Side, No. (%)			.606
Left	24 (49)	21 (44)	
Right	25 (51)	72 (56)	
Saphenous vein, No. (%)			.646
GSV	32 (65)	25 (73)	
AASV	8 (16)	5 (10)	
SSV	9 (18)	8 (17)	
BMI, No. (%) in kg/m^2			<.001†
18-25	10 (20)	31 (65)	
25-30	17 (35)	12 (25)	
>30	22 (45)	5 (10)	
Median height (IQR) in cm	172 (163, 180)	171 (165, 177)	.644
Median weight (IQR) in kg	89 (23)	72 (62, 81)	.001†
Clinical class, No. (%)			.096
C0-C1	5 (10)	7 (15)	
C2-C3	32 (65)	37 (77)	
C4-C6	12 (25)	4 (8)	
Median VCSS (IQR)	5 (4, 8)	4 (3, 6)	.057
Median diameter (IQR) in mm	5 (3, 7)	5 (4, 6)	.532
Varicose veins, No. (%)			
Thigh	20 (41)	13 (27)	.153
Calf	16 (33)	24 (50)	.581
Junction reflux			.591
Yes	34 (70)	34 (71)	
No	11 (22)	12 (25)	
Other	4 (8)	2 (4)	
Median temp inside (IQR) in °	21 (21, 23)	21 (21, 23)	.985
Median temp outside (IQR) in °	14 (9, 20)	15 (9, 19)	.980
Median time visit (IQR) in hr	1200 (1038, 1419)	1100 (919, 1400)	.245
Focal dilatations, No. (%)			.920
0	64 (67)	64 (66)	
≥1	32 (33)	33 (34)	
Refluxing segments, No. (%)			
Proximal	49 (100)	46 (96)	.149
Mid	37 (78)	41 (85)	.219
Distal	35 (71)	35 (73)	.870

<25th percentile was <11% postural diameter change, ≥75th percentile was ≥32% postural diameter change.
[*] Mann-Whitney *U*-test (height, weight, venous clinical severity score (VCSS), diameter, temperature (temp) inside, temp outside, time visit) or χ^2 (age, gender, site, saphenous vein, body mass index (BMI), clinical class, varicose veins, junction reflux, focal dilatations, refluxing segments).
[†] *p*-values remained significant after false discovery rate control.
Abbreviations: GSV, great saphenous vein; AASV, anterior accessory saphenous vein; SSV, small saphenous vein; IQR, interquartile range; hr, hours.

Supplementary Table 2. Multivariable logistic regression of variables associated with ≤25th percentile postural diameter change vs >75th percentile postural diameter change

	Refluxing and healthy legs (*n*=128)	
	Multivariable OR	**95% CI**
Leg		
Control	-	-
Reflux	-	-
Age in years		
<50	1.0	-
50-65	2.1	0.8, 5.9
>65	7.5	2.7, 21.3
Gender		
Females	-	-
Males	-	-
BMI in kg/m^2		
18-25	1.0	-
25-30	1.8	0.6, 5.1
>30	5.8	2.1, 16.2
Clinical class		
C0-C1	-	-
C2-C3	-	-
C4-C6	-	-
Median VCSS (IQR)	1.2	1.0, 1.4
Junction reflux		
Yes	-	-
No	-	-
Median diameter (IQR) in mm	-	-
Focal dilatations		
0	-	-
≥1	-	-

Nagelkerke R^2 of leg model = 0.35.
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; VCSS, venous clinical severity score; IQR, interquartile range.

CHAPTER 4.2

Focal dilatation of the saphenous trunk in chronic venous disease

van der Velden SK
Pichot O
Nijsten T
van den Bos RR
De Maeseneer MGR

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Dear editor,

Focal dilatations of the saphenous trunk (ST) are defined as a dilated part of the ST with a maximal diameter that is 1.5 to 3 times the diameter of the ST above or below.[1] They are commonly reported in patients with great saphenous vein (GSV) reflux and seem to be associated with more advanced stages of chronic venous disease (CVD).[1,2] Understanding the association between focal dilatations and clinical as well as hemodynamic findings may contribute to further unravelling the pathophysiology of CVD. In a cross-sectional cohort study we investigated the distribution of focal dilatations and associated factors in limbs with primary GSV, anterior accessory saphenous vein (AASV), or small saphenous vein (SSV) reflux.

The subjects were recruited from the outpatient clinics of Dermatology (Erasmus MC, Rotterdam) and Angiology (Centre de Médecine Vasculaire, Grenoble) between March 2014 and May 2015. The local Medical Ethical Committee approved the protocol (MEC-2014-035). All patients who gave informed consent underwent a clinical examination, including the clinical class of the CEAP classification[3] and duplex ultrasound scan[4] was performed with the patients standing. Reflux was defined as retrograde flow during >0.5 seconds after calf compression. The presence and number of focal dilatations was registered. The GSV above knee level and the SSV were divided into three equal segments (proximal, mid and distal third) to determine the location of the focal dilatation. A detailed description of the methods was presented previously.[5] Univariable and multivariable logistic regression analysis of the presence of one or more focal dilatations were used to test for associated factors including, gender, age, clinical class, diameter of the ST, and presence or absence of reflux at the junction.

We studied 193 limbs with reflux of either the GSV (73%), SSV (15%) or AASV (12%). Median age was 59 years (interquartile range 22 to 85), and 71% of the patients were women. Most of the included included limbs were classified as C2-C3 (71%). One or more focal dilatations were present in 68 limbs (35%). Two or three focal dilatations in a refluxing ST were less common than one and were only reported in 9% and 4%, respectively, of the study population. Focal dilatations were more often localized in the GSV (43%) than in the SSV (17%) or AASV (5%). In STs with one or more focal dilatations, the dilatation was significantly more often located in the proximal (59%) than in the distal (40%) or mid segment (1%) of the ST ($p < .001$). Of the five included variables, only the diameter of the ST and presence of reflux at the junction were independently associated with the presence of one or more focal dilatations, resulting in a R^2 of 0.21 (Table 1).

Our results confirm that focal dilatations are frequently observed in patients with ST reflux and are associated with junctional reflux and a large saphenous diameter. This demonstrates that presence of one or more focal dilatations is correlated to hemodynamic abnormalities of the refluxing ST. When management strategies in patients with varicose veins are being considered,[6] it should be further investigated whether the

presence in C2 to C3 limbs of one or more focal dilatations, in addition to presence of junctional reflux and a large saphenous diameter, may be an argument for ablation of the refluxing ST rather than its conservation.

Table 1. Univariable and multivariable logistic regression analysis of presence of one or more focal dilatations

	Univariable OR	95% CI	Multivariable OR	95% CI
Age in years				
<50	1.0	-		
50-65	0.7	0.3, 1.5		
>65	0.8	0.4, 1.7		
Gender				
Females	1.0	-	-	-
Males	0.8	0.4, 1.5	-	-
Clinical class				
C0-C1	1.0	-	-	-
C2-C3	1.8	0.7, 4.9	-	-
C4-C6	1.8	0.6, 5.5	-	-
Junction reflux				
Yes	1.0	-	1.0	-
No	0.2	0.1, 0.4	0.3	0.1, 0.7
Diameter	1.5	1.3, 1.8	1.4	1.1, 1.7

Abbreviation: OR, odds ratio; CI, confidence interval

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CHAPTER 5

Predictors for recanalization of the great saphenous vein in randomized controlled trials 1 year after endovenous thermal ablation

van der Velden SK
Lawaetz M
De Maeseneer MGR
Hollestein L
Nijsten T
van den Bos RR
Members of the predictors of endovenous thermal ablation group*

* Biemans AA, Darwood RJ, Disselhoff BC, Helmy ElKaffas K, Lattimer CR, Lurie F, Malskat WS, Atqiaee K, Perälä J, Pronk P, Rasmussen LH, Rass K, van den Bos RR and Vuylsteke M.

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ABSTRACT

Objective: The objective was to identify predictors to develop and validate a prognostic model of recanalization of the great saphenous vein (GSV) in patients treated with endovenous thermal ablation (EVTA).

Methods: The search strategy of Siribumrungwong was updated between August 2011 and August 2014 using Medline, Embase and the Cochrane register to identify randomized controlled trials (RTCs), in which patients presenting with GSV reflux were treated with radiofequency or endovenous laser ablation. Leg-level data (*n*=1226) of 15/23 selected RCTs were pooled. The primary outcome was recanalization of the GSV; the secondary outcome was change in Health-Related Quality of Life (HRQoL) measured by the Chronic Venous Insufficiency quality-of-life Questionnaire (CIVIQ) or Aberdeen Varicose Vein Questionnaire (AVVQ) 1 year post-procedure. Candidate predictors were: age, sex, body mass index, clinical class, GSV diameter, saphenofemoral junction reflux, type of device, energy, and length of treated vein.

Results: At 1 year, 130 GSVs were recanalized (11%). Clinical class (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.4 to 3.3) and diameter (OR 1.8, 95% CI 1.2 to 2.7) of the GSV were the strongest predictors of recanalization. Other predictors included in the final model were sex, type of device and length of treated vein. The performance of the recanalization model was moderate, with an area under the curve above 0.717. GSV diameter, type of device, and amount of energy delivered were the only predictors of the change of HRQoL. None of the candidate predictors were included in the final HRQoL model ($R^2 = 0.027$).

Conclusions: There are several important prognostic factors for GSV recanalization and change of HRQoL after EVTA. However, the performance of each model was unsatisfactory to allow use in clinical practice yet.

INTRODUCTION

In the Western world, endovenous thermal ablation (EVTA) is the most commonly used technique to treat patients with saphenous vein reflux. The therapeutic goal of this technique is to obliterate the treated vein segment by thermal injury to the venous wall.

Although EVTA is highly effective, recanalization of the great saphenous vein (GSV) is reported in up to 10% of patients afer 1 year.[1-3] In these patients, recanalization may be the result of the technique used (e.g., laser or radiofrequency [RF]), device settings (e.g., energy delivered, number of RF cycles) and/or experience of the physician.[4-6] Other factors may also play a role such as patient characteristics, and clinical and duplex ultrasound (DUS) findings.[7,8]

If patient characteristics and DUS findings are indeed associated with the risk of recanalization, physicians might be able to predict which patients are likely to develop recanalization prior to treatment. Identification of patient specific predictors may result in a more personalized approach in phlebologic practice. If patient tailored treatments are offered from the start, the need for extensive secondary procedures could be reduced and health care expenses kept as low as possible.[9]

The objective of this study is to identify patient, DUS and device related characteristics associated with recanalization of the GSV after treatment with EVTA using 1 year follow-up data from multiple randomized controlled trials (RCTs). The secondary objective was to assess factors associated with change of Health-Related Quality of Life (HRQoL) after treatment with EVTA.

METHODS

Data selection

From August 2011 to August 2014, two independent investigators (SKvdV and RRvdB) searched in MEDLINE (OvidSP), Embase, and the Cochrane Central Register of Controlled Trials to identify studies. Search terms were 'varicose veins', 'chronic venous disease', 'chronic venous insufficiency', 'great saphenous vein', 'RF ablation (RFA)', 'RFA', 'endovenous ablation', 'EVTA', 'endovenous laser ablation (EVLA)', 'EVLA', and 'randomized controlled trial'. The identified RCTs were screened for eligibility and combined with the selected RCTs of one recent systematic review of RCTs comparing EVTA and surgical interventions in patients with varicose veins (Supplementary Table 1).[10] Only those RCTs in which patients presented with GSV reflux were randomized to RFA or EVLA were eligible. In addition outcomes regarding GSV patency and/or HRQoL were documented for at least 1 year of follow up. If multiple publications of the same study were present, the study closest to the 1 year follow-up was selected.

Data collection

The investigators contacted the corresponding authors of the 23 eligible RCTs by email between August 2013 and January 2015. For non-responders, a second and third attempt was made a few months later. Five authors were also contacted by phone because of a non-responding after the third e-mail. If available, authors were asked to collaborate and share their patient-level data[11] about age, sex, unilateral or bilateral inclusion, body mass index (BMI) in kg/m^2, clinical class at baseline (C of the CEAP classification), Venous Clinical Severity Score (VCSS), and HRQoL outcomes at baseline and after a follow-up of at least 1 year. DUS data gathered were diameter of the GSV at baseline (mm), presence of saphenofemoral junction (SFJ) reflux at baseline and anatomical outcomes of the treated segment of the GSV (e.g., obliteration, recanalization, absence or presence of GSV reflux). The authors were also asked to share their procedure-related data such as device type and characteristics (wavelength, fiber type, energy delivered [J/cm], number of RF cycles), length of treated segment and additional treatment of tributaries. The earliest year of inclusion was reported and divided into two groups: 2000-2006 or 2007-2013. This cut-off was chosen to obtain an equal distribution of devices in each group and to analyze subsequently the influence of physicians' experience.

Outcomes

The primary outcome measure was recanalization of the GSV after follow-up of at least 1 year. Recanalization was defined as as an open section of the treated vein >5 cm in length. Secondary outcome was changed HRQol at 1 year follow-up compared with baseline (ΔHRQoL). HRQoL questionnaires were defined as instruments that measure objective functioning, subjective well being or both. Disease-specific HRQoL questionnaires were preferred because they often show more sensitivity to change than generic HRQoL questionnaires.[12]

Two disease-specific questionnaires were included to assess quality of life: the Aberdeen Varicose Vein Questionnaire (AAVQ) and the Chronic Venous Insufficiency Questionnaire (CIVIQ). Total scores of both questionnaires ranked between 0 and 100, with 0 representing the most favorable HRQoL. Therefore, AAVQ and CIVIQ outcomes were pooled and analyzed together.

Candidate predictors

Candidate predictors were selected based on the available data. Patient characteristics at baseline (e.g., age, clinical class and BMI), DUS features (diameter of the GSV and presence of SFJ reflux) and technical aspects of treatment (e.g., device, length of treated segment, energy delivered and number of RF cycles) were considered as important predictors of recanalization and ΔHRQoL. VCSS and additional treatment of tributaries were recorded for <50% of the limbs and therefore not considered as candidate predictors.

Study population

Corresponding authors from 15 (response rate 65%) different EVTA RCTs in Europe,[1,3,13-21] the USA,[16] Asia,[22] and Africa[23] agreed to collaborate (Supplementary Table 2). Of the excluded RCTs, five authors refused to participate, two authors were non-contactable, and one author had lost the study data. The included RCTs were conducted in secondary care populations between 2000 and 2013. If outcome measures were missing, leg-level data were excluded (*n*=142 in the anatomical cohort and *n*=798 in the HRQoL cohort; Figure 1). In the HRQoL cohort, for each patient only one leg was included. Finally, 1226 legs (1174 patients) were included in the anatomical cohort and 537 legs (537 patients) in the HRQoL cohort.

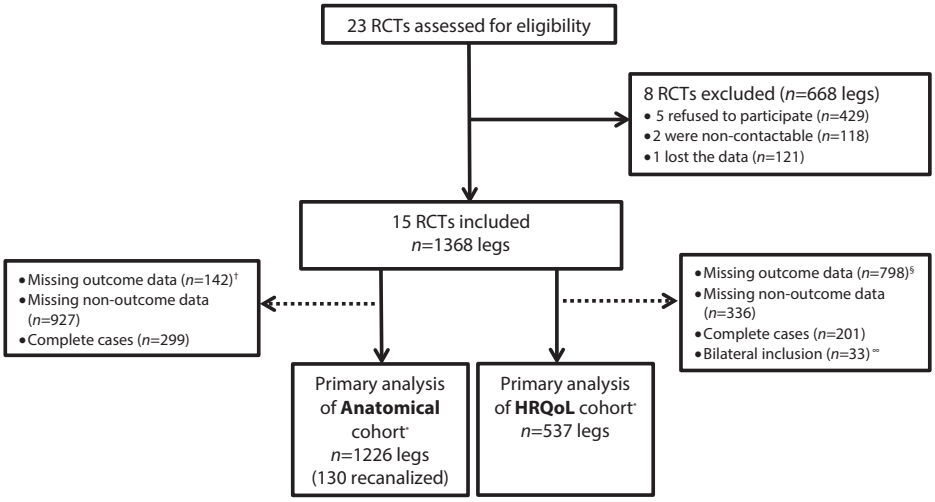

Figure 1. Flow diagram of included studies and legs

† No data available regarding anatomical (e.g., recanalization) or § Health-Related Quality of Life (HRQoL) outcomes at 1 year follow-up. * Analyzed using multiple imputation methods. ∞ In patients in whom both legs were randomized to EVTA, only one leg was included in the HRQoL analysis.

Abbreviation: RCT, randomized controlled trial.

Statistical analysis

Multivariable regression modeling techniques were used to predict recanalization and HRQoL. The initial study design was to split the complete dataset into a development dataset and an external validation dataset. Owing to the low number of events (i.e., development dataset *n*=93, external validation dataset *n*=37) it was decided to develop the model using the complete dataset. Therefore the model could be validated internally, but not externally.

Missing data in non-outcome data was addressed by multiple imputation with chained equations to create 40 complete datasets (i.e., 40% was the maximum percent-

age of missing data for both the anatomical and the HRQoL cohorts; Table 1).[24] All available variables were included in the multiple imputation model. Any predictor recorded for <50% of legs was not included in further uni- and multivariable analysis.

All variables of the univariable analysis were included as candidate predictors. Predictors of recanalization of the GSV were analyzed using multivariable logistic regression and multivariable linear regression was used to predict ΔHRQoL. Possible non-linearity of the predictors and the outcome was addressed using restricted cubic splines (with three knots). Backward stepwise selection based on the Akaike's information criterion was used for both regression models (corresponding p = .157). The discriminative performance of the model (i.e., how well the model can discriminate between patients with and without recanalization) was assessed in terms of the area under the curve (AUC) or R^2 using bootstrap samples (n=1000). Models having AUC values >0.8 have some utility in predicting the response of individual subjects.[25] The regression coefficients in the final model were multiplied by a shrinkage factor (calibration slope) to prevent over-optimistic regression coefficients, which would lead to too extreme predictions on future data.

Categorical variables were compared using χ^2 or Fischer exact test. Continuous variables were analyzed using the Mann-Whitney *U*-test. The Bonferroni test was used to correct for multiple testing.

Statistical analysis was performed using SPSS, version 21.0 (IBM, Armonk, NY, USA) and R version 2.15.2. (http://www.R-project.org).

RESULTS

In the anatomical cohort, 130 recanalization events (11%) were reported over a mean ± standard deviation (SD) follow-up period of 1.0 ± 0.2 years among 1174 participants. Mean ± SD follow-up in the HRQoL cohort was 1.0 ± 0.0 years and 91% of patients reported some improvement of HRQoL. The main study characteristics of the anatomical and HRQoL cohort are summarized in Table 1.

Recanalization (anatomical cohort)

Univariable analysis

For the different candidate predictors analyzed, odds ratios (OR) and 95% confidence intervals (CI) of recanalization 1 year after EVTA are summarized in Table 2 (univariable analysis). The odds of recanalization were lower for legs of women than men. Legs with C3-C6 disease had a two to three times higher odds of developing recanalization than legs with C2 disease. The same was true for presence of SFJ reflux, with higher odds than for absence of SFJ reflux.

Table 1. Baseline characteristics of included legs

	Anatomical cohort				HRQoL cohort
	Total (*n*=1226)	*Recanalization* (*n*=130)	*Obliteration* (*n*=1096)	*p-value*[*]	*Total* (*n*=537)
Start inclusion, No. (%)				<.001	
2000-2006	382 (31)	57 (44)	325 (30)		168 (31)
2007-2013	844 (69)	73 (56)	771 (70)		369 (69)
Missing	0	0	0		0
Median age in years (IQR)	51.9 (40-62)	51.0 (39-62)	52.0 (40-62)	.563	52.0 (40-64)
Missing, No. (%)	0	0	0		
Sex, No. (%)				<.001	
Males	407 (33)	62 (48)	345 (32)		170 (32)
Females	818 (67)	68 (52)	750 (68)		367 (68)
Missing	1 (0)	0	0		0
Median BMI in kg/m^2 (IQR)	25.1 (23, 28)	27.1 (25, 29)	25.0 (23, 28)	.003	24.6 (23, 28)
Missing, No. (%)	519 (42)	70 (54)	449 (41)		233 (43)
Bilateral legs, No. (%)	104 (9)	7 (5)	97 (10)	.462	0
Missing	-	-	-		
Clinical class, No. (%)				<.001	
C2	690 (56)	43 (33)	647 (59)		374 (70)
C3-C6	463 (38)	74 (57)	389 (35)		151 (28)
Missing	73 (6)	13 (10)	60 (6)		12 (2)
SFJ reflux, No. (%)				.082	
Yes	922 (75)	112 (86)	810 (74)		517 (96)
No	74 (6)	4 (3)	70 (6)		8 (1)
Missing	230 (19)	14 (11)	216 (20)		12 (2)
Median GSV diameter in mm (IQR)	6.8 (6, 8)	8.0 (6, 10)	6.6 (6, 8)	<.001	7.0 (6, 9)
Missing, No. (%)	78 (6)	8 (6)	70 (6)		56 (10)
Device, No. (%)					
RFA	205 (16)	24 (19)	181 (16)	2.476	130 (24)
810nm	242 (20)	37 (28)	205 (19)	.048	109 (20)
940nm	233 (19)	40 (31)	193 (18)	<.001	73 (14)
980nm	266 (22)	16 (12)	250 (23)	.032	181 (34)
1470nm	280 (23)	13 (10)	267 (24)	<.001	44 (8)
Missing	-	-	-	-	-
Median energy in J/cm (IQR)	56.2 (43, 66)	54.6 (43, 64)	56.4 (43, 66)	.598	62.6 (47, 74)
Missing, No. (%)	351 (29)	32 (25)	319 (29)		256 (48)
Median length of treated vein in cm (IQR)	36.7 (30, 43)	35.9 (28, 45)	36.8 (30, 43)	.176	38.0 (30, 42)
Missing, No. (%)	247 (20)	31 (24)	216 (2)		168 (31)

[*] Mann-Whitney *U*-test (age, body mass index [BMI], great saphenous vein [GSV] diameter, energy and length of treated vein), χ^2 test (inclusion period, bilateral legs, clinical class, saphenofemoral junction [SFJ] reflux), χ^2 test with Bonferroni post-hoc testing (site of diameter measurement, device).

Abbreviations: IQR, interquartile range; HRQoL, Health-Related Quality of Life; RFA, radiofrequency ablation.

Multivariable analysis

Sex, clinical class, SFJ reflux, diameter, type of device, and length of treated vein remained independent predictors of recanalization (Table 2, multivariable analysis). ORs of the multivariable analysis were comparable with those of the univariable analysis, except for SFJ reflux (OR 2.6 *versus* 0.6). In the internal validation of the model, only SFJ was deleted resulting in an AUC of 0.717, suggesting low levels of utility.

Table 2. Association between each predictor and recanalization

	Univariable		**Multivariable**		
	OR (95% CI)	*p-value*	*OR (95% CI)*	*β*	*Shrunken β[#]*
Intercept	NA	NA	0.02 (0.02, 0.3)	−3.8	−3.5
Sex		<.001			
Males	1.0		1.0	0	0
Females	0.5 (0.4, 0.7)		0.6 (0.4, 0.9)	−0.6	−0.5
Age in years	0.99 (0.98, 1.01)	.393	-	-	-
BMI in kg/m^2	1.04 (0.99, 1.09)	.155	-	-	-
Clinical Class		<.001			
C2	1.0		1.0	0	0
C3-C6	2.6 (1.7, 3.8)		2.1 (1.4, 3.3)	0.8	0.7
SFJ		.066			
No reflux	1.0		1.0	0	0
Reflux	2.6 (0.9, 7.1)		0.6 (0.4, 7.8)	1.0	0.8
GSV diameter in mm *(6 vs 8)*[¶]	2.0 (1.4, 3.0)	<.001[*]	1.8 (1.2, 2.7)	0.6	0.5
Device		<.001			
RFA	1.0		1.0	0	0
810nm	1.4 (0.8, 2.4)		1.1 (0.6, 2.0)	0.06	0.05
940nm	1.6 (0.9, 2.7)		1.5 (0.8, 0.8)	0.4	0.4
980nm	0.5 (0.3, 0.9)		0.5 (0.2-1.0)	−0.7	−0.6
1470nm	0.4 (0.2, 0.7)		0.4 (0.2-0.8)	−1.1	−0.9
Energy in J/cm	1.0 (0.98, 1.01)	.552	-	-	-
Length of treated vein in cm *(30 vs 43)*[¶]	0.9 (0.7, 1.1)	.007[*]	0.8 (0.6, 1.0)	−0.3	−0.3

Anatomical cohort was analyzed using univariable logistic regression. Health-Realted Quality of life (HRQoL) cohort was analyzed using linear regression. The variables included in the multiple imputation model were age, sex, body mass index (BMI), clinical class, diameter of the great saphenous vein (GSV), site of diameter measurement, device (e.g., radiofrequency of laser wavelength), length of treated segment, energy delivered, number of cycles, Venous Clinical Severity Score and HRQoL scores at baseline, reflux of the GSV and recanalization of the GSV. In the HRQoL cohort, Δ HRQoL was also included in the multiple imputation.
[#] Regression coefficient multiplied with a shrinkage factor. [¶] Values are nonlinear, therefore, odds ratio (OR) and β were calculated using the interquartile range of the original dataset. * *p*-values of total factor.
Abbreviations: CI, confidence interval; NA, not applicable; SFJ, saphenofemoral junction; RFA, radiofrequency ablation.

ΔHRQoL (HRQoL cohort)

Univariable analysis

ORs for HRQoL improvement 1 year after EVTA treatment are summarized in Table 3 (univariable analysis). If SFJ reflux was present at baseline, patients reported more HRQoL improvement than in cases when there was no SFJ reflux. HRQoL scores improved more after treatment with RFA than after treatment with any laser device.

Table 3. Association between each predictor and Δ HRQoL

	Univariable		**Multivariable**	
	β (95% C.I)	*p-value*	*β (95% CI)*	*Shrunken β#*
Intercept	NA	NA	−20.6	−18.3
Sex		.725	-	-
Males	0			
Females	0.4 (−1.7, 2.5)			
Age in years *(40 vs 62)*¶	0.3 (−1.3, 1.8)	.316*	-	-
BMI in kg/m^2 *(23 vs 28)*¶	0.02 (−3.0, 3.1)	.827*	-	-
Clinical Class		.531	-	-
C2	0			
C3-C6	−0.7 (−2.8, 1.5)			
SFJ		.293	-	-
No reflux	0			
Reflux	−4.4 (−12.5, 3.8)			
GSV diameter in mm	−0.3 (−0.9, 0.3)	.285	−0.4 (−1.0, 0.2)	−0.3
Device		<.001		
RFA	0		0	0
810nm	2.4 (−0.5, 5.2)		3.8 (−0.2, 7.8)	3.3
940nm	6.0 (2.8, 9.2)		5.5 (1.6, 9.4)	4.8
980nm	7.0 (4.5, 10.0)		6.4 (2.9, 9.9)	5.6
1470nm	4.3 (0.5, 8.1)		3.2 (−1.2, 7.7)	2.9
Median Energy in J/cm *(47 vs 74)*¶	3.5 (1.0, 6.0)	.116*	2.7 (−0.5, 5.9)	2.4
Length of treated vein in cm *(30 vs 42)*¶	−0.8 (−2.2, 0.8)	.490*	-	-

Anatomical cohort was analyzed using univariable logistic regression. Health-Related Quality of Life (HRQoL) cohort was analyzed using linear regression. The variables included in the multiple imputation model were age, sex, body mass index (BMI), clinical class, diameter of the great saphenous vein (GSV), site of diameter measurement, device (e.g., radiofrequency of laser wavelength), length of treated segment, energy delivered, number of cycles, Venous Clinical Severity score and HRQoL scores at baseline, reflux of the GSV and recanalization of the GSV. In the HRQoL cohort, Δ HRQoL was also included in the multiple imputation.

Regression coefficient multiplied with a shrinkage factor. ¶ Values are nonlinear, therefore, β was calculated using the interquartile range of the original dataset. *p-values of total factor.

Abbreviations: CI, confidence interval; NA, not applicable; SFJ, saphenofemoral junction; RFA, radiofrequency ablation.

Multivariable analysis

In the multivariable analysis of the HRQoL cohort, only the diameter of the GSV, type of device and delivered energy were predictors for ΔHRQoL, but the CI remained large (Table 3, multivariable analysis). Patients who were treated with any laser device reported less improvement of their HRQoL than patients who were treated with RFA. In the internal validation of the model all factors were deleted, resulting in a R^2 of 0.027 and thus indicating a poor fit of the model.

Recanalization related to changed HRQoL (HRQol cohort)

At 1 year follow-up, median change of HRQoL score in patients without recanalization of the GSV (−10.3, interquartile range [IQR] −17.5 to −4.6) was not different from patients with recanalization (−8.8, IQR −17.5 to −2.6) (p = .368) (Figure 2).

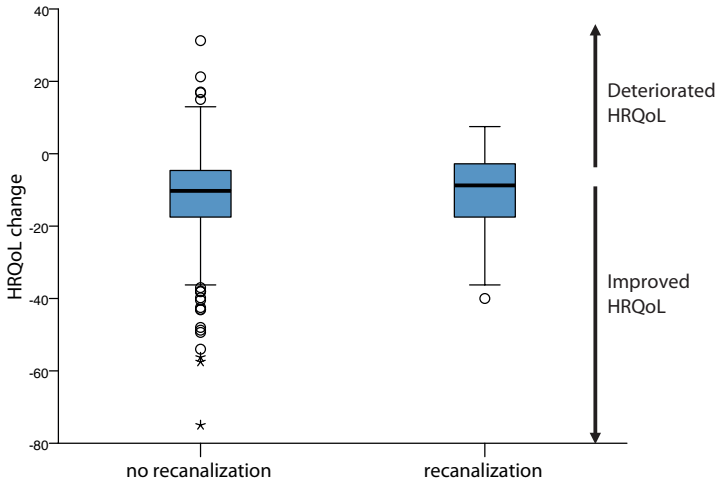

Figure 2. Boxplot of Δ Health-Related Quality of Life (HRQoL) in patients without recanalization (n=486) and with recanalization (n=51)

DISCUSSION

This study shows that sex, clinical class, SFJ reflux, GSV diameter, length of treated vein, and type of device are independent predictors of recanalization of the GSV after EVTA. The diameter of the GSV, type of device, and energy level independently influenced the degree of improvement in HRQoL. Although several independent predictors of recanalization and HRQoL were found, their predictive ability was too low to allow application in clinical practice.

The finding that male sex is an independent predictor of GSV recanalization after EVTA is contrary to previous findings. Two prospective studies considered sex as a pre-

dictor of recanalization, but this was not confirmed in multivariable analysis.[7,26] Although no evidence was found in the literature to explain the male predominance in risk of recanalization, it could be hypothesized that the vein wall of males is thicker than the vein wall of females.

Legs with C3-C6 disease were more likely to develop recanalization than legs with C2 disease. In patients with varicose veins, it has been shown that the tunica intima and tunica media are significantly thicker than in controls.[27] Limbs with clinical class C3-C6, defined as chronic venous insufficiency (CVI) according to the Vein-Term consensus document,[28] develop higher venous pressure in the legs and are therefore more prone to remodeling of the venous wall.[27,29] Thickening of the vein wall may result in less effective transmural damage with subsequent recanalization of the vein after EVTA. The finding that patients with CVI are more at risk of developing recanalization emphasizes the importance of DUS screening at an early stage of the disease and in the presence of venous symptoms.

Several authors suggested an association between obesity and recanalization or recurrence.[7,9,26] Excess weight results in a relative obstruction of venous return with subsequent increased venous filling pressures.[32] In the present study, BMI was not found to be a predictor of recanalization. However, in total only 8.7% patients (95 limbs) with a BMI >30 kg/m^2 were included and this might have caused underestimation of the influence of BMI on recanalization.

The presence of SFJ reflux was an independent predictor of recanalization in the multivariable analysis but it was no longer a predictor in the internal validation. One explanation could be the low number of patients without SFJ reflux (74 legs) because most RCTs only included patients with SFJ reflux.

The finding that GSV diameter is an independent predictor of recanalization is in line with previous findings.[8,26] Veins with a greater diameter might be more prone to recanalization because of the increased amount of intraluminal blood or distance between the tip of the laser fiber and the vein wall. Therefore, adequate application of tumescent anesthesia and Trendelenburg position are important to reduce the diameter of the vein.[30]

The likelihood of recanalization decreased with the use of higher wavelengths lasers (e.g., 980nm or 1470nm), suggesting the improved efficacy of more recently developed EVLA systems. This was confirmed by finding a statistically significant difference in recanalization between inclusions before and after 2007, with less recanalization in limbs included after 2007 when higher wavelengths were increasingly used. In addition, the experience of physicians with endovenous procedures might have increased over time. Unfortunately, correlation between year of treatment and device could not be investigated because newer devices were not available before 2006.

In the present study, overall HRQoL scores improved after treatment with EVTA, irrespective of the development of recanalization at 1 year follow-up. One small prospective trial showed clinical and hemodynamic improvement 1 month after single ambulatory phlebectomies, even in presence of persisting GSV reflux.[31] The independent improvement of HRQoL scores was also illustrated by the extremely low predictive ability of the HRQoL model, as GSV diameter, type of device, and delivered energy were the only weak predictors of HRQoL in the multivariable analysis. However, in the internal validation of the HRQoL model, all predictors were removed from the model. This is in line with a previous prospective cohort study, assessing factors associated with changed HRQoL scores in patients with saphenous reflux, in which they found no correlation between changed AVVQ scores and venous hemodynamics six weeks after RFA.[32]

The AUC of 0.717 and R^2 of 0.027 is unsatisfactory to allow application of the prediction models in clinical practice yet.[25] Future research should update the final models, preferably in a large prospective longitudinal cohort study, by incorporating new candidate predictors in order to improve performance of the prediction models. Other factors such as experience of physicians, VCSS, additional treatment of tributaries, persisting SFJ reflux after a procedure,[33] or development of new refluxing tributaries due to progression of the disease over time may contribute to the development of recanalization.[34] In addition, comorbidities may influence HRQoL over time. Although a variety of study designs can be used to develop a prediction model,[35] only randomized studies were included because of the standardized reporting, decreased selection bias and low numbers lost to follow-up 1 year post-procedure.

Recently, the European Society for Vascular Surgery developed clinical practice guidelines for the management of patients with CVD.[36] In the future physicians should combine these clinical guidelines with patient specific predictors, to optimize their management decisions for the individual patient with CVD.

This study has several limitations. First is the lack of external validation of the final models, and therefore generalizability of the models remains uncertain. Second, the generalizability of the developed models might be affected by some exclusion criteria of this RCT cohort. Several studies did not represent the entire varicose vein population because legs with C3-C6 disease or large diameter saphenous vein (>12 mm) were excluded.[4,14-16,18,19] Hence, a large prospective cohort representing a large variety of varicose vein patients should be used to update and validate the models. Third, the predictive ability of the models might have been caused by low number of events (causing a limited degree of freedom), exclusion of candidate predictors (e.g., VCSS or additional treatment of tributaries), or presence of non-registered predictors (e.g., comorbidity, persisting SFJ reflux or new tributaries).

In conclusion, this study implies that there are several predictors for recanalization after EVTA. For the change of HRQoL 1 year after treatment with EVTA, GSV diameter, the

type of device used, and amount of energy delivered appeared to be the only predictors. However, the performance of each model was unsatisfactory and therefore cannot be used in clinical practice.

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SUPPLEMENTARY

Supplementary Table 1. Search strategy of Siribumrungwong

Search period	2000 to August 2011
Sources	MEDLINE and Scopus
Study selection	Two independent reviewers
Search terms	('varicose veins'[Mesh], 'saphenous vein'[Mesh], varicose and saphenous), (radiofrequency, RFA, VNUS,'endovenous laser', EVLT, EVLA, sclerotherapy[Mesh], 'foam sclerotherapy', microfoam, stripping and sapheno-femoral ligation) and (obliteration, occlusion, recurrence, recurrent, recanalisation, neovascularization, reflux, pain, 'return to normal activities', 'return to work', haematoma, paresthesia, 'nerve injury', 'wound infection', deep vein thrombosis (DVT) and thromboembolism)
Inclusion criteria	Randomized controlled trials, comparison of outcomes between any of the minimally invasive endovenous procedures (MIEPs) and surgery or between MIEPs in patients with great saphenous vein reflux, reported at least one outcome of interest.
Exclusion criteria	Non-English written studies or insufficient data

Supplementary Table 2. Study characteristics.

Study	Country	Type of device and anesthesia	Inclusion criteria	Exclusion criteria*	Site of diameter measure-ment	HRQoL tool (range)	Definition of treatment success
Biemans 2013 (*n*=75)	Nether-lands	940-nm, bare fibre Tumescent	Adult patients with a symptomatic primary GSV reflux at least above the knee with a diameter of >0.5 cm and SFJ reflux	Deep venous reflux or obstruction, vascular agenesis, use of anticoagulation, pregnancy, heart failure, immobility, ABI <0.6), inability to provide written informed consent	At mid-thigh	CIVIQ (0-100)	Complete obliteration, without flow or reflux. Recanalization rate: 31%
Darwoord 2006 (*n*=12)	UK	810-nm, fibre unknown Tumescent	Adult patients (>18 years) with symptomatic varicose veins and primary SFJ reflux	Use of warfarin or unsuitable for EVLA (tortuous GSV, large incompetent anterior accessory saphenous vein).	Unknown	AVVQ (0-100)	Abolition of GSV reflux in the treated segment (e.g., absence of retrograde flow on both color flow). Occlusion: absent flow in a non-compressible vein Recanalization rate: 0%
Disselhoff 2008 (*n*=58)	Nether-lands	810-nm, bare fibre Tumescent	Patients with primary symptomatic uncomplicated varicose veins (e.g., C2 disease), aged 19–75 years, with SFJ and GSV reflux from the groin to below the knee	History of DVT, deep venous reflux, reflux in below-knee perforating veins, duplication of the GSV	At mid-thigh	AVVQ (0-100)	Incompetent GSV (an open section of the treated segment over 5 cm in length, with reflux >0.5). Explanation only reported in 5y. Recanalization rate: 0%

Supplementary Table 2. (continued)

Study	Country	Type of device and anesthesia	Inclusion criteria	Exclusion criteria*	Site of diameter measure-ment	HRQoL tool (range)	Definition of treatment success
Elkaffas 2011 (*n*=45)	Egypt	VNUS closure system Tumescent	Patients with SFJ and GSV reflux (reversed venous flow >0.5 seconds)	DVT, SVT, use of anticoagulants, PAD, pacemakers, serious systemic disease, pregnancy, GSV diameter >18 mm in the thigh or extremely tortuous veins	Unknown	-	Saphenous vein was ablated or removed with no flow from within 5 cm of the SFJ to the knee. Failure if flow was present in segments greater than 10 cm distal to the SFJ. Recanalization rate: 27%
Lattimer 2013 (*n*=44)	UK	1470-nm, bare fibre Tumescent	Patients with symptomatic varicose veins, SFJ reflux (>0.5 s), suitable for either EVLA or UGFS	SPJ reflux, deep venous reflux, recurrent disease, GSV diameter >12 mm, previous surgery or SCT, previous or acute DVT, known coagulopathy, ABI <0.8, active malignancy, pregnancy, known allergy to local anesthetic or sclerosing agents	Mean of three measurements: 2 cm below the SFJ, at mid-thigh and 5 cm above the popliteal skin crease	AVVQ (0-100)	GSV occlusion. Recanalization rate: 9%
Lurie 2005 (*n*=25)	Austria, France, USA	VNUS closure system Tumescent or general	Patients aged between 21 and 80 years, with GSV reflux (>0.5 s), C2-C4 disease, ambulatory status, GSV diameter <12 mm in supine position, availability for follow-up visits. Segmental deep reflux was allowed.	GSV diameter <0.2 mm, duplication of GSV, AASV or SSV reflux, varices of the thigh, previous DVT, ABI <0.9), axial deep venous reflux, tortuosity of the GSV segment to be treated	At mid-thigh	CIVIQ (0-100)	Less than 5 cm of GSV patency from the SFJ, with the distance measured from the junction along the curve of the GSV to the proximal obliteration point. Recanalization rate: 20%

Supplementary Table 2. (continued)

Study	Country	Type of device and anesthesia	Inclusion criteria	Exclusion criteria*	Site of diameter measure-ment	HRQoL tool (range)	Definition of treatment success
Malskat (*n*=132)	Nether-lands	940-nm, tulip fibre 1470-nm, tulip fibre Tumescent	Adult patients (>18 years) with primary GSV reflux (>0.5 sec), saphenous vein diameter >5 mm and C2-C6 disease	Pregnancy, immobility, acute DVT or SVT, agenesis of the deep venous system, vascular malformation, PTS of the obstructive type, PAD and allergy to lidocaine.	At mid-thigh	-	Complete obliteration, without flow or reflux Recanalization rate: 12%
Mozafar 2013 (*n*=30)	Iran	980-nm, fibre unknown Tumescent	Patients with symptoms of CVI, SFJ reflux and GSV reflux at least to knee level, aged 18-65 years.	Pregnancy, active malignancy, ABI <0.8, acute DVT, thrombophilia or high risk of pulmonary thromboemboli, history of inguinal surgery except for hernia, ipsilateral SSV reflux	At the SFJ	AVVQ (0-100)	Recurrence or recanalization Recanalization rate: 7%
Rautio 2001 (*n*=15)	Finland	VNUS closure system General	Patients suitable for day-case surgery with symptomatic, previously untreated, and uncomplicated GSV tributary varicosis and isolated unilateral SFJ and GSV trunk reflux	Coagulopathy or multiple, tortuous, and large-diameter (>12 mm) GSV trunks	Maximum diameter	-	Occlusion of treated GSV segment Recanalization rate: 7%
Pronk 2010 (*n*=61)	Nether-lands	980-nm, bare fibre Tumescent	Patients aged >18 years, C2-C6 disease, GSV and SFJ reflux, length of GSV >15cm (measured from the SFJ downwards) and GSV diameter between 3-5mm.	Previous surgical treatment of the GSV, pregnancy, immobility, intolerance of lidocaine, active SVT, previous or active DVT, deep venous reflux	At knee level	-	The ability to compress the GSV, or presence of reflux (>0.5 s) in a vein originating in the groin and connecting with the femoral vein. Recanalization rate: 10%

Supplementary Table 2. (continued)

Study	Country	Type of device and anesthesia	Inclusion criteria	Exclusion criteria*	Site of diameter measure-ment	HRQoL tool (range)	Definition of treatment success
Rasmussen 2010 (*n*=55)	Denmark	980-nm, bare fibre Tumescent	Patients with symptomatic varicose veins, aged 18-80 years, C2-C4 disease and GSV reflux (>0.5 s).	Duplication of the GSV, reflux of AAGSV or SSV, deep vein reflux, previous DVT, arterial insufficiency, tortuous GSV	3 cm below the SFJ	AVVQ (0-100)	Closed or absent GSV. Recanalization of the GSV was defined as an open section of the treated vein >5 cm in length. Recanalization rate: 5%
Rasmussen 2011 (*n*=240)	Denmark	980-nm, bare-tip fibre 1470-nm, bare fibre VNUS closure system Tumescent	Patients with symptomatic varicose veins, aged 18-80 years, C2-C4 disease and GSV reflux (>0.5 s)	Duplication of the GSV, reflux of AAGSV or SSV, deep vein reflux, previous DVT, arterial insufficiency, tortuous GSV	3 cm below the SFJ	AVVQ (0-100)	Closed or absent GSV. Recanalization of the GSV was defined as an open section of the treated vein >5 cm in length. Recanalization rate: 4%
Rass 2012 (*n*=172)	Germany	810-nm, bare fibre Tumescent	Patients with SFJ and GSV reflux at least down to the knee level, symptoms and/or CVI caused by GSV reflux, aged 18-65 years and performance status class I-II.	Previous surgical interventions in the groin area with the exception of inguinal herniotom, ipsilateral AASV, PASV or SSV reflux, acute deep DVT or PTS, known thrombophilia, ABI <0.8, active malignant disease (diagnosed during the past 5 years), poor compliance or inability to understand the study-related procedures, pregnancy or nursing	At the SFJ	CIVIQ (0-100)	Clinical recurrence defined as new varices linked to saphenofemoral recurrence, to an incompetent GSV or perforator at medial thigh level. Recurrence rate at the SFJ and treated GSV were defined as reflux at the SFJ (vessels >2.0 mm diameter) and reflux at the GSV over a distance of at least 2 cm distally from the SFJ. Recanalization rate: 22%

Supplementary Table 2. (continued)

Study	Country	Type of device and anesthesia	Inclusion criteria	Exclusion criteria*	Site of diameter measure-ment	HRQoL tool (range)	Definition of treatment success
van den Bos 2014 (*n*=92)	Nether-lands	940-nm, bare fibre Tumescent	Patients aged >18 years with symptomatic primary reflux of the GSV (>0.5 s) and diameter >5mm.	Acute DVT or SVT, agenesis of the deep venous system, vascular malformation, PTS of the obstruction type, pregnancy, immobility, allergy to lidocaine or ABI <0.9	At mid-thigh	-	Obliteration of treated segment and/or absence of reflux. In analysis chosen for obliteration. Recanalization rate: 7%
Vuylsteke 2012 (*n*=170)	Belgium	1470-nm, bare fibre Tumescent	Patients with functional and/ or aesthetic inconvenience, aged >18 years and GSV reflux.	Ipsilateral reflux of the SSV and/or AASV, deep venous reflux, GSV diameter >15 mm and crossdilatation with two or more incompetent side-branches, use of therapeutical anticoagulation or hypocoagulopathy, hypercoagulopathy or thrombophilia, ABI <0.85) or pregnancy	Mean of three points: 2 cm distal to the SFJ, mid-thigh and knee level.	-	Occlusion rate was categorized by the GELEV score. 0= no occlusion, refluxing vein. 1a= partial occlusion with proximal reflux. 1b=partial occlusion without reflux. 2a= complete occlusion with unchanged or larger diameter. 2b= complete occlusion with diameter reduction >30%. 3=complete occlusion with diameter reduction >50%. 4=fibrotic cord, vein not visible. We encoded 2a, 2b,2c,3 and 4 into success. Recanalization rate: 2%

* If duplication with inclusion criteria existed, the exclusion criteria was removed.

Abbreviations: HRQoL, health related quality of life; GSV, great saphenous vein; SFJ, saphenofemoral junction; ABI, ankle-brachial index; CIVIQ, Chronic Venous Insufficiency Questionnaire; UK, United Kingdom; EVLA, endovenous laser ablation; SPJ, saphenopopliteal junction; AVVQ, Aberdeen Varicose Vein Questionnaire; DVT, deep venous thrombosis; SVT, superficial venous thrombosis; PAD, peripheral arterial disease; UGFS, ultrasound-guided foam sclerotherapy; SCT, sclerocompression therapy; USA, United States of America; AASV, anterior accessory saphenous vein; SSV, small saphenous vein; PTS, post-thrombotic syndrome; CVI, chronic venous insufficiency; AAGV, anterior accessory great saphenous vein; PASV, posterior accessory saphenous vein.

CHAPTER 6.1

Management strategies for patients with varicose veins (C2-C6): results of a worldwide survey

van der Velden SK
Pichot O
Van den Bos RR
Nijsten T
De Maeseneer MGR

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ABSTRACT

Objective: This study evaluated how patient characteristics and duplex ultrasound findings influence management decisions of physicians with specific expertise in the field of chronic venous disease.

Methods: Worldwide, 346 physicians with known interest and experience in phlebology were invited to participate in an online survey about management strategies in patients with great saphenous vein (GSV) reflux and refluxing tributaries. The survey included two basic vignettes representing a 47 year old healthy male with GSV reflux above the knee and a 27 year old healthy female with a short segment refluxing GSV (CEAP classification C2sEpAs2,5Pr in both cases). Participants could choose one or more treatment options. Subsequently, the basic vignettes were modified according to different patient characteristics (e.g., older age, morbid obesity, anticoagulant treatment, peripheral arterial disease), clinical class (C4, C6) and duplex ultrasound findings (e.g., competent terminal valve, larger or smaller GSV diameter, presence of focal dilatation). The authors recorded the distribution of chosen management strategies; adjustment of strategies according to characteristics; and follow-up strategies.

Results: A total of 211 physicians (68% surgeons, 12% dermatologists, 12% angiologists, and 8% phlebologists) from 36 different countries completed the survey. In the basic case vignettes 1 and 2, respectively, 55% and 40% of participants proposed to perform endovenous thermal ablation, either with or without concomitant phlebectomies ($p <$ .001). Looking at the modified case vignettes, between 20% and 64% of participants proposed to adapt their management strategy, opting for either a more or a less invasive treatment, depending on the modification introduced. The distribution of chosen management strategies changed significantly for all modified vignettes ($p < .05$).

Conclusion: This study illustrates the worldwide variety in management preferences for treating patients with varicose veins (C2-C6). In clinical practice, patient related and duplex ultrasound related factors clearly influence therapeutic options.

INTRODUCTION

Numerous successful treatment options are available for patients with uncomplicated and complicated varicose veins. These treatment options include thermal, chemical, or surgical ablation of the refluxing saphenous trunk(s) with or without high ligation, phlebectomies or (foam) sclerotherapy of refluxing tributaries, and combinations of the above. As a result of the many available options, physicians may treat patients in many different ways. This may also cause some difficulties in selecting the best management strategy. Physicians have to decide whether to proceed to a more or less invasive treatment, or even refrain from treatment. Several factors will influence this decision: experience and preference of the physician, presence of symptoms, Health-Related Quality of Life (HRQoL), severity of the chronic venous disease (CVD) and other patient related and duplex ultrasound (DUS) characteristics, as well as patients' preference.[1,2] Physicians obviously need to evaluate both the potential risks and benefits of any treatment they are considering, as well as the costs.[3]

To determine a proper management strategy in patients with CVD, physicians are usually referred to current guidelines like those of the Society for Vascular Surgery and the American Venous Forum.[4] They clearly state that 'the scientific evidence must be combined with the physician's clinical experience to select the best treatment option for each individual patient'.[4-6] Apart from guidelines, there are not many other useful tools available for assisting physicians to optimize their management strategy for the individual patient.

The objective of this survey was to evaluate more detailed criteria regarding patient characteristics, clinical and DUS findings, which may influence management decisions in patients presenting with uncomplicated or complicated varicose veins.

METHODS

Participants

The investigators contacted all national presidents of member societies of the International Union of Phlebology (Union Internationale de Phlébologie [UIP]), from 43 different countries between July and August 2013. Worldwide, these 'key contacts' were asked to nominate 10-20 physicians (vascular surgeons, angiologists, dermatologists, phlebologists) per country who were known to have an interest in phlebology and had been performing varicose vein treatments for at least 5 years. If the president of the national phlebologic society could not be contacted, another colleague from the same country was contacted.

Physicians were considered eligible if they were familiar with the use of several currently used varicose veins treatment techniques, including phlebectomies, one of the techniques for endovenous thermal ablation (EVTA), and ultrasound-guided foam sclerotherapy (UGFS). They were also allowed to participate if they did not perform EVTA themselves, but delegated this to a colleague when indicated. The same was true for high ligation and stripping.

All nominated physicians were invited by email to complete the online survey between January and March 2014. The survey was available in English and Spanish.

Survey

At the beginning of the survey, participating physicians were asked for their specialty, their practice (which techniques they perform themselves, and for which they refer a patient to a colleague), years of experience in treating phlebologic patients, country of education, and country of present clinical practice.

The survey further included two basic case vignettes of patients with great saphenous vein (GSV) reflux. Basic case vignette (V1) reported the case of a 47 year old healthy man (body mass index [BMI] 23.4 kg/m^2) who presented with heaviness of the right leg. Physical examination of the legs demonstrated varicose veins without edema or skin changes on the right leg. DUS examination (Figure 1) revealed reflux from the terminal valve at the saphenofemoral junction (SFJ) and GSV reflux above the knee. The diameter of the GSV was 6 mm at mid-thigh level. Refluxing tributaries (largest diameter, 5 mm) were seen at medial calf level. There was no GSV reflux below the knee. The deep venous system was patent and competent. The CEAP classification was C2SEpAs2,5Pr.

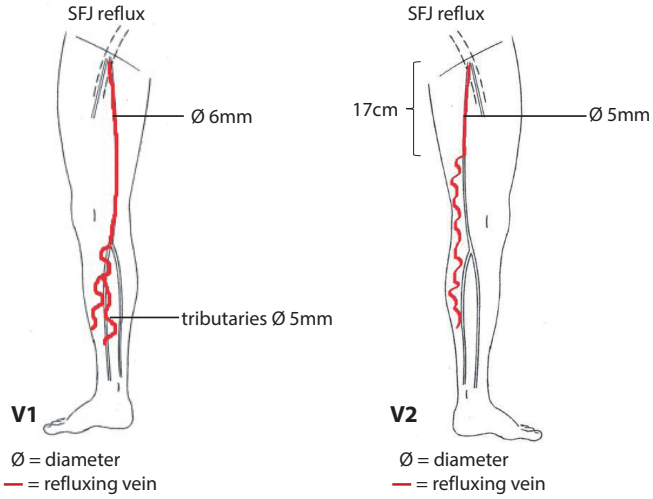

Figure 1. Overview of duplex ultrasound findings of basic case vignette 1 (V1) and 2 (V2)
Abbreviation: SFJ, saphenofemoral junction.

Following the description of V1, participants were first asked which management strategy they would like to perform in this patient. To answer this question, they were able to choose one or more of the 10 proposed potential answers, including EVTA, ligation and stripping, single stripping (also called isolated stripping), UGFS of the GSV, UGFS of the tributaries, concomitant phlebectomies, isolated phlebectomies, CHIVA (Cure Hémodynamique de l'Insuffisance Veineuse en Ambulatoire, a particular surgical treatment based on hemodynamics),[7] medical elastic compression stockings (MECS), no treatment, or 'other', to be specified by the respondent, if the preferred treatment option was not one of the 10 above cited possibilities.

Subsequently, V1 was modified step by step, changing complaints, patient characteristics, clinical findings and DUS findings (Table 1). Participants were then asked whether they would change their strategy for the modified case and, if so, to indicate which treatment option(s) they would prefer. Participants were also asked to determine cut-off values for GSV diameter, below which or above which they would change their

Table 1. Modifications of basic case vignettes in the survey

Case vignette 1 (C2SEpAs2,5Pr):
Complaints:
asymptomatic, only cosmetic concern (C2AEpAs2,5Pr)
Patient characteristics:
older age >80 yrs
gender: female
peripheral arterial disease (ankle brachial index <0.6)
high body mass index (>40 kg/m^2)
chronic oral anticoagulant treatment
Clinical findings:
skin changes – pigmentation (C2,4aSEpAs2,5Pr)
venous ulceration (C2,6SEpAs2,3,5Pr)
Duplex ultrasound findings:
competent terminal valve
focal dilatation of GSV above knee (12 mm)
small diameter of GSV (cut-off value determined by participant)
large diameter of GSV (cut-off value determined by participant)
Case vignette 2 (C2SEpAs2,5Pr):
Duplex ultrasound findings:
diameter of short refluxing segment <5 mm
diameter of short refluxing segment >8 mm
length of refluxing GSV segment (cut-off value determined by participant)

abbreviation: GSV, great saphenous vein

treatment strategy. Only cut-off values between 1-13 mm were further investigated in the survey.

After completion of the questionnaire concerning all the modifications of V1, a second basic case vignette (V2) was described: a 27 year old healthy female (BMI 23 kg/m^2) complaining of heaviness and fatigue of the left leg. She presented with varicose veins in the medial thigh extending to the calf, without edema or skin changes. DUS (Figure 1) revealed reflux of the GSV, from the terminal valve of the SFJ, to 17 cm below the SFJ. At this level, the GSV had a large refluxing tributary, while the GSV itself became very small without any reflux. The diameter of the cranial refluxing GSV segment was 5 mm. CEAP classification was defined as C2SEpAs2,5Pr.

Finally, participating physicians were questioned about the timing of the first follow up after the initial treatment and whether they want to schedule further visits or not. They were further asked to indicate which of the following parameters would influence their management strategy for persisting refluxing tributaries after successful ablation of the GSV: clinically visible or not, large or small diameter, superficial course or not, cosmetic complaints or not, presence or absence of symptoms, and clinical class, according to the CEAP classification.

Statistics

The McNemar test was used to compare paired proportions of preferred treatment options between the basic vignette and modified vignettes. The Bonferroni test was used to correct for multiple testing. The change in distribution of management strategies between the basic case vignettes and modified case vignettes was compared using the Stuart-Maxwell test, which is used to compare paired proportions with more than two categories.

To be included in the analysis, a particular treatment strategy had to be chosen by at least 5% of all respondents. Options or combinations of options chosen by less than 5% were summarized as 'alternative' in the global analysis.

Multivariable logistic regression analysis investigated the association between physicians' characteristics and the preferred treatment strategy (e.g., surgical *versus* non-surgical). Independent variables included time since certification, continent of clinical practice, and specialty. To prevent overfitting, a limited number of independent variables were included.

The Statistical Package for the Social Sciences (SPSS), version 21.0 software (IBM, Armonk, NY, USA) was used for data analysis. The distribution analyses were conducted using available software (http://www.R-project.org).

RESULTS

A total of 211 specialists from 36 different countries completed the survey (Table 2), resulting in a response rate of 58%.

Basic case vignettes

Participants chose a variety of different strategies for both V1 and V2 (Table 3). In V1 and V2, respectively 55% and 40% of participants proposed to perform EVTA, either with or without concomitant phlebectomies ($p < .001$). In V2 11% preferred single phlebectomies as initial treatment, compared with only 6% in V1 ($p = .01$).

Multivariable logistic regression analysis only revealed a significant association between the duration since certification (<20 years) and a less invasive treatment strategy (e.g., UGFS or EVTA of the GSV, conservative or no treatment) (data not shown).

Table 2. Characteristics of physicians participating in the survey

Characteristics	*n*(%)
Specialty	
Surgeon (mostly vascular)	143 (68)
Dermatologist	26 (12)
Angiologist	25 (12)
Phlebologist	17 (8)
Certified since	
<10 years	25 (12)
10-20 years	72 (34)
>20 years	114 (54)
Continent of current clinical practice	
Europe	147 (70)
Latin America	30 (14)
Asia	13 (6)
North America	10 (5)
Oceania	11(5)
Techniques performed in own practice	
EVTA	167 (79)
UGFS	182 (86)
Surgery	152 (59)
Phlebectomies	165 (78)
CHIVA	31(15)

Abbreviations: EVTA, endovenous thermal ablation; UGFS, ultrasound-guided foam sclerotherapy; CHIVA, conservative hemodynamic treatment.

Table 3. Treatment strategies proposed by the participants for the basic case vignettes 1 (V1) and 2 (V2)

Treatment strategies	V1 *n*(%)	V2 *n*(%)
EVTA	43 (20)	16 (8)
EVTA + phlebectomies	73 (35)	67 (32)
EVTA + UGFS of tributaries	17 (8)	9 (4)
Ligation + stripping + phlebectomies	12 (6)	10 (5)
EVTA + ligation	13 (6)	15 (7)
UGFS of GSV + UGFS of tributaries	9 (4)	11 (5)
Single phlebectomies	5 (2)	23 (11)
Alternative	39 (19)	60 (28)

Abbreviations: EVTA, endovenous thermal ablation; UGFS, ultrasound-guided foam sclerotherapy, GSV, great saphenous vein.

Modified case vignettes

The main results of the survey regarding changes in proportion of the different management strategies in the modified case vignettes are summarized in Figures 2 and 3.

Interestingly, for most patient and DUS related factors, the change in distribution of management strategies between the basic vignettes and modified vignettes was significant.

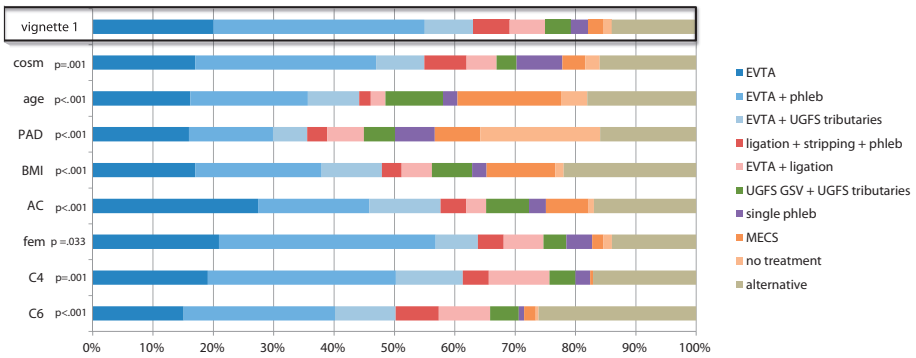

Figure 2. Influence of cosmetic complaints, patient characteristics and clinical findings on management strategy (*n*=211)

p-values represent the difference in distribution between vignette 1 and modified vignettes (only cosmetic complaints [cosm], age, peripheral arterial disease [PAD], body mass index [BMI], anticoagulant treatment [AC], female gender [fem], C4, C6) and were measured using Stuart-Maxwell test.

Abbreviations: EVTA, endovenous thermal ablation; phleb, phlebectomies; UGFS, ultrasound-guided foam sclerotherapy; GSV, great saphenous vein; MECS, medical elastic compression stockings.

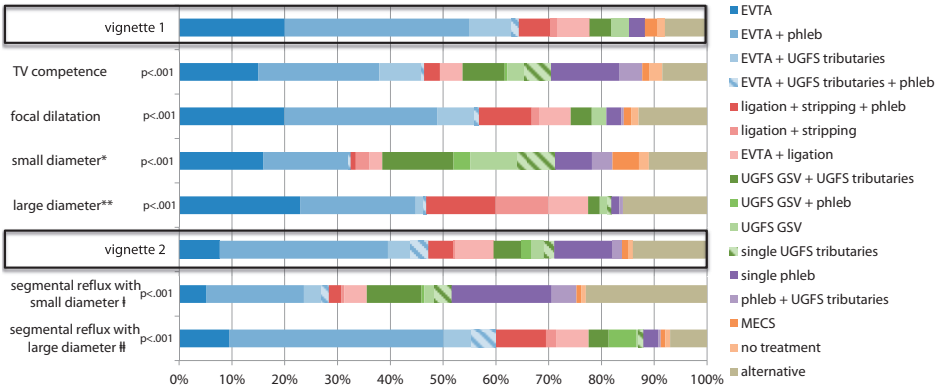

Figure 3. Influence of duplex ultrasound findings on management strategy

p-values represent the difference in distribution between vignette 1 and modified vignettes (terminal valve [TV] competence, focal dilatation, small diameter, large diameter) or between vignette 2 and modified vignettes (segmental reflux with small diameter, segmental reflux with large diameter) and were measured using Stuart-Maxwell test.

* *n*=155, small diameter was based on the cut-off value for diameter of the great saphenous vein (GSV) below which participants would consider to change their treatment strategy (median 4 mm). ** *n*=138, large diameter was based on the cut-off value for diameter of the GSV above which participants would consider changing their treatment strategy (median 10 mm). ǂ For this question of the survey, small diameter of segmental refluxing GSV was defined as <5 mm by the investigators. ǂǂ Large diameter of segmental refluxing GSV was defined as >8 mm.

Abbreviations: EVTA, endovenous thermal ablation; phleb, phlebectomies; UGFS, ultrasound-guided foam sclerotherapy; MECS, medical elastic compression stockings.

Patient characteristics (Figure 2)

Looking at the different patient characteristics (Table 1), older age, peripheral arterial disease (PAD), and high BMI were considered relevant in altering the management strategy in respectively 61%, 64%, and 52% of participants. In the vignettes with one of these three patient characteristics modified, a quarter of participants proposed to convert their strategy into a less invasive treatment, mainly consisting of fewer phlebectomies, more UGFS of tributaries, and more MECS. In particular, in cases of PAD 'no treatment' became a frequently preferred option (20%). Physicians who indicated they would prescribe MECS for patients with PAD as an alternative treatment usually added this would be a 'light' compression stocking. Several participants answered they would first opt for an arterial revascularization. For patients with high BMI putting them on a diet, in addition to other conservative measures was often suggested. The use of oral anticoagulant treatment (coumarin) was a reason for adapting the treatment strategy for 45% of participating specialists, and this mainly consisted of avoiding phlebectomies. Female gender clearly appeared to be less important for adapting the management strategy, as only 26% of respondents stated they would do so.

Clinical findings

If the clinical class of V1 was modified from C2 (varicose veins) to C4a (pigmentation), the preferred treatment technique(s) did not change considerably. However, if the patient suffered from venous ulceration (C6), with GSV reflux extending down to the ankle, participants avoided phlebectomies and were more likely to consider another additional treatment (e.g., high ligation, UGFS of the GSV below the knee and/or UGFS of tributaries).

Duplex ultrasound findings

If the terminal valve was competent, fewer participants would ablate or remove the refluxing GSV. Instead, 13% preferred single phlebectomies ($p < .001$).

Presence of a focal dilation of the GSV did not result in a major shift of treatment strategy although the distribution of treatments altered significantly compared to the basic vignette ($p < .001$).

A vast majority of respondents (74%) answered that vein diameter was important for the treatment strategy. They changed their management when the diameter of the GSV was less than a median of 4 mm (interquartile range [IQR] 3-5) or above 10 mm (IQR 7-10). If the diameter of the GSV was below 4 mm, 44% of participants indicated a change to a less invasive treatment compared to V1. If the diameter was above 10 mm, more EVTA with additional high ligation or classic surgery was proposed, representing 31% of all options.

The patient of V2 had GSV reflux from the terminal valve, only limited to a short segment of the GSV. If the diameter of the short refluxing GSV segment was modified to <5 mm, a change to a less invasive treatment was observed. If the short segment had a diameter >8 mm, participants less frequently selected single phlebectomies ($p < .001$) and more often EVTA with or without phlebectomies ($p < .001$).

Only 39% of the participants considered the length of refluxing trunk relevant for deciding whether or not to ablate the trunk. They suggested a minimal length of at least 10 cm (minimum 2 cm, maximum 45 cm).

Follow-up and further treatment

Seventy-one per cent of participants replied they would evaluate the immediate outcome of the proposed management strategy within 8 weeks after initial treatment. The majority claimed to continue follow-up thereafter for various reasons (Figure 4).

Over 60% of physicians proposed to treat persistent refluxing tributaries, in cases where there were symptoms, cosmetic concerns, or visible tributaries (Figure 5). Phlebectomies seemed to be used as frequently as UGFS to treat refluxing tributaries. However, there was a preference for phlebectomies in cases where tributaries had a large diameter, a superficial course, or where they were visible, and a preference for UGFS in other cases ($p < .001$) (Figure 5).

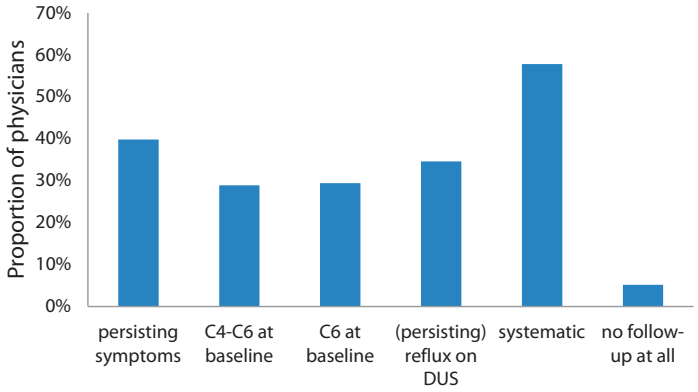

Figure 4. Reasons for further visits after initial follow-up
Systematic was defined as 'I would schedule patients for further follow up visits, irrespective of symptoms, physical and/or ultrasound examination'.
Abbreviation: DUS, duplex ultrasound.

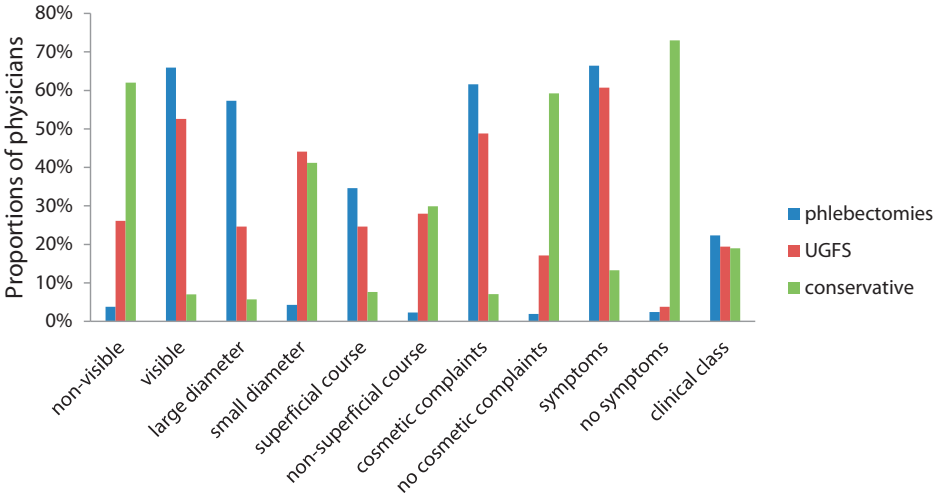

Figure 5. Influence of different characteristics of persisting refluxing tributaries on the preferred management strategy
Abbreviations: UGFS, ultrasound-guided foam sclerotherapy

DISCUSSION

The results of this survey first of all illustrate that physicians all over the world use many different management strategies for treating patients with varicose veins. Second, EVTA has become a very popular option for treating patients with uncomplicated varicose

veins with GSV reflux. Third, patient characteristics, clinical findings and DUS findings influence management decisions in patients presenting with varicose veins, as expected.

The large diversity in treatment methods may be partially explained by differences in available resources and/or health care policies in different countries, for example equipment, reimbursement of certain interventions, timing (treatment only allowed in one session, or in multiple sessions), and setting (hospital environment or private practice). However, when comparing the results among the participating continents or specialties, no major differences could be found. In 2006, a survey on the management of varicose veins was distributed among the members of the Vascular Society of Great Britain and Ireland. Only half of the respondents offered the same range of treatment in their National Health Service (NHS) and private practice. This was mainly due to restrictions for the treatment of varicose veins in their NHS practice.[8]

National and international guidelines for the management of chronic venous disorders, have only become available in recent years. Interestingly, the results of the present survey revealed that participants use several single or combined treatment strategies which are not cited in any guideline, and are not supported by the literature, for example adding high ligation to EVTA,[9] and some of the treatment strategies belonging to the 'alternative' group. Probably, in varicose vein treatment, as in other specialties, it might be useful to establish recommendations about 'do nots', to avoid overuse or misuse of procedures, potentially leading to harm or unnecessary health care spending. In the United States, an interesting initiative has been launched in 2012 by the American Board of Internal Medicine Foundation, who initiated the 'Choosing Wisely' campaign (http:// choosingwisely.org) to improve appropriate and necessary treatment. So far, about 60 specialty societies have published a 'List of Five Things Physicians and Patients Should Question', consisting of five recommendations about what should not be done. Unfortunately, no recommendations have been made for 'choosing wisely' in patients with varicose veins.

The EVTA option was very popular in both basic case vignettes. Nowadays, EVTA has largely replaced classic surgery as the treatment of choice for the incompetent GSV, and classic extensive surgery under general anesthesia can no longer be considered the gold standard.[10] After 100 years of status quo, it is surprising how fast minimally invasive endovenous treatment methods have been accepted worldwide.[11]

According to the survey, several patient characteristics influenced management strategies, in particular older age, concomitant PAD, high BMI, and oral anticoagulant treatment. Older age resulted in a shift towards a less invasive treatment, with more participants choosing UGFS, MECS, or no treatment for uncomplicated varicose veins. This seems logical, in view of comorbid conditions and often limited mobility in elderly patients.

If severe PAD was present, participants were more likely to adapt their treatment strategy to a more conservative treatment (e.g., no treatment or light compression stockings). It was quite surprising to find several physicians prescribing MECS in a patient with an ankle-brachial index <0.6, although some of them clearly stated they would do so only after arterial revascularization. Two prospective studies reported a safe application of 'modified' compression therapy (not by means of stockings, but with inelastic material and reduced compression pressure of 20-30 mmHg) in patients with moderate PAD (ankle brachial pressure index between 0.8 and 0.5).[12,13] Nevertheless, extreme caution is necessary when compression is applied to legs with severe PAD to prevent skin necrosis.[14]

For patients with a high BMI, participants in the survey more frequently suggested conservative measures, in comparison to V1 (patient with a normal weight). Several studies stated that patients with a higher BMI are more likely to develop surgical site infections and anatomic failures after groin surgery or radiofrequency ablation.[15,16] Hence it seems logical to have these patients lose some weight before proceeding to endovenous or surgical treatment of varicose veins. If the patient was on chronic anticoagulant treatment, participants often avoided performing phlebectomies. In these patients phlebectomies may indeed exceptionally lead to major bleeding complications, in particular when large tributaries and perforating veins are involved.[17] Therefore, it may be wise to limit the number of phlebectomies, monitor International Normalized Ratio, employ local anesthetic with adrenaline, or even tumescent anesthesia.[17] There are less concerns about treating patients on anticoagulation with EVTA or UGFS.[18,19]

As the majority of participants already recommended an intervention in the C2 patient of V1, it is not surprising to see no real changes in management of a patient with C4a, except for adding high ligation to truncal ablation. The same was true for C6 patients, apart from the many alternative options suggested by the participants. DUS findings did alter treatment strategy, and it was mainly the diameter of the refluxing GSV trunk that was considered relevant. The presence of a focal dilatation of the trunk only led to minor changes in strategy in the present survey. According to a recently published retrospective study, terminal valve incompetence, a greater diameter of the GSV in the thigh, and the presence of a focal dilatation of the GSV were found significantly more frequently in cases treated by ablation of the GSV than in those treated with phlebectomies only (ASVAL method = ambulatory selective varices ablation under local anesthesia).[20]

GSV diameter was considered important in management decisions. Large diameter GSVs are almost always associated with terminal valve incompetence at the SFJ, and are related to increased hemodynamic impairment, and higher clinical class (C4-C6).[21,22] Recently, a randomized controlled trial, comparing UGFS with classic surgery, showed that patients with a large diameter GSV and distal GSV reflux at baseline had a higher probability of failure after UGFS.[23] On the other hand, according to several retrospective

studies, particularly focusing on the early outcome after EVTA in larger veins (with a diameter >10 or >12 mm), no difference could be found in efficacy (obliteration rate) between these larger veins and those with a smaller diameter.[24,25]

In the case of a small diameter of the refluxing GSV almost one-third of participants indicated they would proceed to UGFS of the GSV and/or tributaries, or single phlebectomies without GSV ablation. One large prospective study demonstrated that UGFS of saphenous veins is more efficient in veins smaller than 6 mm diameter than in those with larger diameters.[26] Single phlebectomy has been investigated in two prospective studies, which showed abolition of reflux after single phlebectomies in the case of smaller diameter GSVs, a short refluxing GSV segment, clinical class C2, and relatively low impact of CVD on HRQoL before treatment.[27,28]

This study has a number of limitations. First of all, characteristics of non-responders were not recorded. Therefore, the authors were not able to exclude the presence of a selection bias. Second, as the survey was only available in English and Spanish, difficulties with the language may have been an issue. Third, two important participant characteristics were not recorded: work setting (hospital or private practice) and reimbursement of phlebologic care in country of present practice. These characteristics might have influenced the variety of treatment preferences.

In conclusion, this study illustrates the worldwide variety in management preferences for treating patients with varicose veins (C2-C6). In clinical practice, patient related and DUS related factors clearly influence therapeutic options.

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CHAPTER 6.2

A personalized management strategy for patients with chronic venous disease: results of a Delphi consensus

van der Velden SK
van den Bos RR
Pichot O
Nijsten T
De Maeseneer MGR

Submitted for publication.

ABSTRACT

Objective: To obtain consensus on management criteria for symptomatic patients with chronic venous disease (CVD; clinical class C2-C6) and superficial venous reflux and subsequently to develop a management strategy flowchart incorporating these criteria.

Method: We used a Delphi method by means of statements sent by email over the course of three rounds. The statements addressed criteria for endovenous ablation (EVA), ultrasound-guided foam sclerotherapy (UGFS), high ligation and stripping (HL/S), single phlebectomies and non-interventional measures (e.g., venotonic drugs and medical elastic compression stockings) in patients with different characteristics (e.g., extensive comorbidities, morbid obesity and peripheral arterial disease). Experts in the field of phlebology from across the world rated 35 statements on a 1 to 9 scale. If at least 70% of the ratings for a specific statement were between 7-9 (agreement) or between 1-3 (disagreement), experts' consensus was reached. Statements remaining equivocal were returned to the experts in a subsequent round until consensus was reached. Only statements with consensus could be included in the final flowchart.

Results: Twenty-five experts were invited to participate, of whom 24 accepted and completed all three rounds. Consensus was reached in 25/32 statements (78%). Experts agreed on all statements regarding indications for treatment with EVA, HL/S and non-interventional measures. Several statements addressing UGFS, single phlebectomies, patients with extensive comorbidities and morbid obesity remained equivocal. A management strategy flowchart for legs with CVD (C2-C6) and symptomatic venous reflux was proposed.

Conclusion: Considerable consensus was reached within a group of experts but also some gaps in available research were highlighted. The proposed flowchart may be the first step towards personalized treatment of patients with CVD.

INTRODUCTION

Over the past decades, numerous effective treatments have been developed for patients with chronic venous disease (CVD). The increased availability of different treatment options has made the management of CVD more complex and challenging. It has resulted into a large worldwide variety in management preferences for treating patients with CVD.[1,2] Management strategies are not only based on evidence from the literature, but also on the physician's own experience, availability (and costs) of the equipment and on national health care reimbursement systems. However, in clinical practice, management decisions should ideally be influenced mainly by a combination of patient characteristics, clinical findings and results of duplex ultrasound (DUS).[1,3,4]

Although there are several well-established national and international guidelines,[5-8] their recommendations only focus on the treatment of a diseased population rather than an individual patient.[9] Appropriate tools for management strategies incorporating the specific characteristics of an individual patient, as well as the clinical and DUS findings, are lacking in current clinical guidelines.[5-8] A practical tool, like an easily applicable flowchart, may assist physicians to optimize their management decision in CVD patients and hence improve phlebologic care for individual patients. To bridge the gap between current clinical guidelines and personalized care, expert opinion methods such as a Delphi consensus[10] are desired.

The aim of the present study was to achieve an international Delphi based consensus of management criteria for patients presenting with venous symptoms, clinical signs of CVD, and superficial venous reflux confirmed by DUS, resulting in a flowchart.

METHODS

Expert panel

Experts were selected from a group of physicians who already participated in our recently published worldwide survey on management strategies in patients with CVD (C2-C6).[1] Only those with at least one scientific publication in the field of phlebology in a peer-reviewed journal and at least ten years of experience in treating patients with CVD were eligible for the present study. They had to be performing ultrasound-guided foam sclerotherapy (UGFS), endovenous thermal ablation (EVTA) and phlebectomies themselves. Two investigators (SvdV and MDM) selected the expert panel. For this selection, they aimed at having a reasonable distribution between different specialties (vascular or general surgeons, dermatologists, angiologists, phlebologists) and continent or country of clinical practice. Based on the selection criteria 25 eligible experts were invited by email. They were asked to judge on several statements in view of obtaining consensus

over the course of three rounds, according to the Delphi method between March 2015 and November 2015 (Figure 1). In case of non-responding, the investigators sent two email reminders in each round.

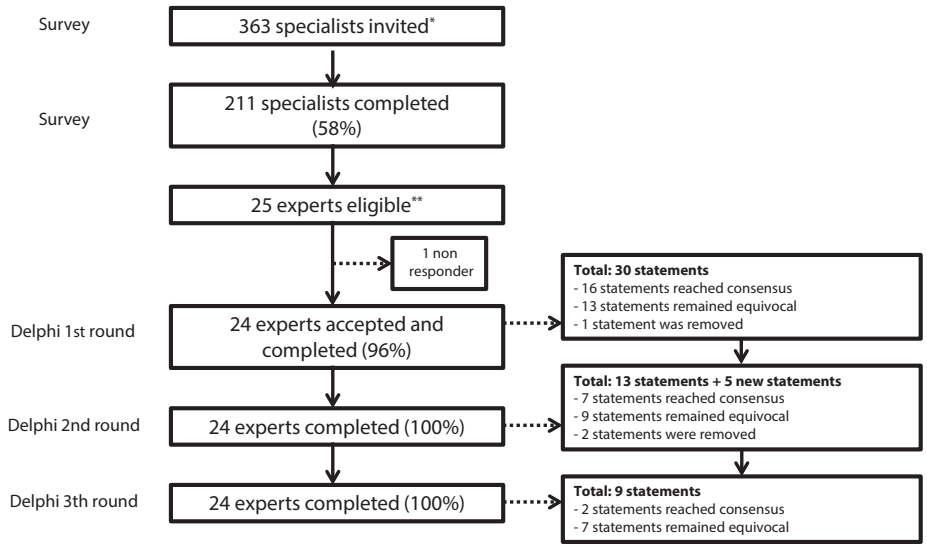

Figure 1. Selection of participants for the Delphi consensus

* Eligibility criteria: performing varicose vein treatments for at least five years and familiar with the use of several currently used varicose veins techniques including, phlebectomies, one of the techniques for endovenous thermal ablation, and ultrasound-guided foam sclerotherapy. They were also allowed to participate if they did not perform EVTA themselves, but delegated this to a colleague when indicated. The same was true for high ligation and stripping.

** Eligibility criteria: at least one scientific publication in a phlebologic peer-reviewed journal, at least ten years of experience in treating phlebologic patients and performing ultrasound-guided foam sclerotherapy, endovenous thermal ablation and phlebectomies themselves.

Delphi consensus procedure

The authors formulated the statements, using results from a worldwide survey regarding management strategies in patients with great saphenous vein (GSV) and tributary reflux.[1] The first round contained 30 statements addressing criteria for endovenous ablation (thermal and non-thermal techniques), UGFS, high ligation and stripping (HL/S), single phlebectomies without treatment of the refluxing saphenous trunk (ST) referred to as 'ambulatory selective varicose ablation under local anesthesia' (ASVAL)[11] and non-interventional measures (venotonic drugs and medical elastic compression stockings [MECS]). The statements contained scenarios with different patient characteristics, clinical class (C2-C6 according to the CEAP classification[12]) and DUS findings in patients with CVD of the lower limbs and superficial venous reflux in a saphenous trunk (ST). The terminology used for the statements is summarized in Table 1.

Table 1. Definition of terminology used for the statements of the Delphi consensus

Venous symptoms:	ache, pain, heaviness, tightness, feeling of swelling, nocturnal cramps, itching
C disease:	clinical class according to the CEAP classification[1]: C2: varicose veins; C3: edema; C4: skin changes (pigmentation, eczema, atrophie blanche, lipodermatosclerosis); C5: healed venous ulcer; C6: open venous ulcer
Saphenous trunk:	great saphenous vein, anterior accessory saphenous vein, posterior accessory saphenous vein, Giacomini vein, small saphenous vein
Varicose tributaries:	visible or palpable varicose veins in the subcutis
Reflux in a saphenous trunk:	abnormally reversed flow in a saphenous trunk, during >500 ms at calf compression-release or Valsalva (the latter only for the SFJ) involving the terminal or preterminal valve of the SFJ or the SPJ
Terminal valve reflux:	reflux at the junction of the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ)
Segmental reflux:	reflux limited to a segment of a saphenous trunk, not involving the SFJ or SPJ
Saphenous diameter:	diameter measured in a tubular part of the refluxing vein segment, about 15 cm from the junction in standing position
Focal dilatation:	localized dilatation of the saphenous trunk less than 1.5–3 times the saphenous diameter above or below
Aneurysm:	dilatation of the saphenous vein more than 3 times the saphenous diameter above or below, or more than 20 mm (close to the SFJ or SPJ)
Morbid obesity:	Body mass index (BMI) >40kg/m^2 or BMI >35kg/m^2 and experiencing obesity-related health conditions
Severe peripheral arterial disease:	ankle brachial index <0.6
Bridging:	oral anticoagulation is interrupted with bridging anticoagulation, using either heparin or low molecular weight heparin, administered during the sub-therapeutic window.

[1]Eklöf B, Rutherford RB, Bergan JJ, et al; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004;40(6):1248-52.

Participants were asked to anonymously rate each statement on a 9-point scale, by ticking boxes with marks between 1 and 9, where a score of 1 denoted complete disagreement and a score of 9 indicating full agreement (Figure 2). If at least 70% of the ratings for a specific statement were between 7-9, it was concluded experts consented on agreeing with the statement. Vice versa, if ≥70% were between 1-3, it was concluded they consented on disagreeing with the statement.[13,14] Any other distribution of ratings was valued 'equivocal'. Participants also had the opportunity to add a comment in the 'remark(s)' box accompanying each statement. All this information was used for preparing the subsequent round of the Delphi consensus.

In the second round, experts received a full report of the first round, including a compilation of ratings for all statements of the first round, and all the remarks of their colleagues, provided anonymously. Then they were asked to rate again those statements that had remained equivocal in the first round. Statements were reformulated and new

statements were added based on the remarks of the experts in the previous round. For instance, in the first round we had included older age as a patient characteristic, which might influence management. However, participating experts suggested age was not the main factor, but rather extensive comorbidities, and therefore the statement was adapted as such. Eventually the second round contained 18 statements. In the second round we also attached a summary of the present literature regarding each statement.

The same procedure was followed for the third (and last) round, which contained only nine statements to be rated. Again, participating experts could consider the results of the second round and the remarks of their colleagues.

In case of one or more missing items, the expert was contacted by email to retrieve the missing answer.

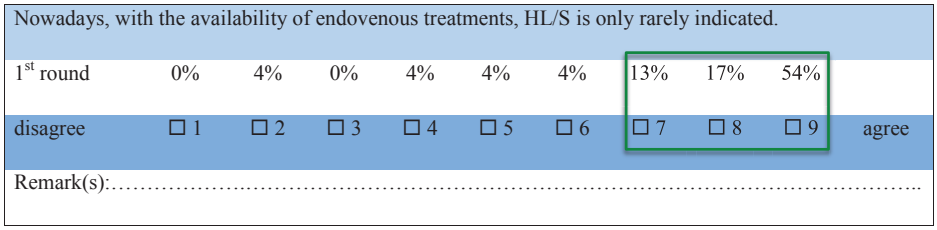

Figure 2. Example of a statement showing consensus on agreement (84% of marks between 7-9). Abbreviation: HL/S, high ligation and stripping.

Constructing a flowchart

Based on the experts' opinion processed in the Delphi consensus a flowchart for management of lower limbs with CVD (C2-C6) and ST reflux was constructed, taking into account patient characteristics, clinical class (divided into C2-C3 and C4-C6) and presence or absence of varicose tributaries. In addition, the following DUS criteria were considered: terminal valve reflux, presence of reflux of the ST or only segmental reflux, diameter of the refluxing ST, varicose tributaries and presence of a focal dilatation or venous aneurysm. For each of the possible management strategies in the flowchart the most appropriate strategy as well as potential alternative treatments were suggested, in agreement with the results of the Delphi consensus.

RESULTS

Experts

In total, 24 out of 25 contacted experts accepted to participate: 15 vascular surgeons, two general surgeons, four dermatologists, two angiologists and one phlebologist from Europe (67%), Oceania (4%), North-America (17%) and Central- or South- America (12%).

All these experts completed the first, second and third Delphi round (100%). The majority of experts (63%) had over 20 years of experience in treating patients with CVD. About half of the experts were working in private practice, the other half either in a general or university hospital.

Delphi consensus

After three rounds, consensus was reached in 25 out of 32 statements (78%; Table 2).

All statements regarding indications for treatment with thermal or non-thermal endovenous ablation (EVA) *versus* treatment with HL/S reached high (>79%) consensus in favor of EVA, except for venous aneurysms. Of note, 96% of the experts agreed on that high ligation should not be added to EVA treatment. Similar level of agreement was reported about the use of MECS as preferred strategy in those patients with C4-C6 disease and reflux in a ST, who are not willing or contraindicated to undergo any intervention.

The experts' opinion on several statements remained equivocal after three rounds. This was the case for statements addressing different indications for UGFS, ASVAL, extensive comorbidities and morbid obesity. The experts stated it depended on the type and extent of the patient's comorbidities and therefore no definitive conclusion on preferred management could be made. Regarding morbid obesity the experts would definitely prefer EVA over HL/S, but there was no agreement on limiting treatment to those patients with skin changes (C4-C6). Moreover, based on their experience, the participants were convinced that advising weight reduction unfortunately was unsuccessful in the majority of obese patients.

Throughout the different rounds of the Delphi consensus three statements were removed, two because of redundancy after reformulating other statements and one because of lack of relevance following the experts' remarks (Supplementary Table 1).

Flowchart

The proposed management strategy for lower limbs with CVD (C2-C6), and symptomatic reflux of a ST has been summarized in a flowchart (Figure 3). The flowchart is not all-inclusive because more factors than those integrated in the flowchart presented could affect patient care.

DISCUSSION

The present study showed that considerable consensus could be reached within a group of selected experts in the field of treatment of superficial venous disease, by means of a Delphi consensus procedure. This allowed us to construct a comprehensive flowchart,

Table 2. Results of Delphi consensus

Statements	Delphi rounds		
	1	2	3
EVA versus HL/S			
Nowadays, with the availability of endovenous treatments, HL/S is only rarely indicated.	84%		
In case of saphenous reflux, EVA is indicated rather than HL/S, even if there is C4-C6 disease.	83%		
In patients with venous symptoms and reflux in a saphenous trunk, EVA is indicated rather than HL/S, even in the presence of TV reflux.	83%		
In patients with venous symptoms and reflux in a saphenous trunk, EVA is indicated rather than HL/S, even in the presence of a large (>10 mm) saphenous diameter.	79%		
In patients with venous symptoms and reflux in a saphenous trunk, EVA is indicated rather than HL/S, even in the presence of one or more focal dilatations.	79%		
Presence of a venous aneurysm (>20 mm) within 2 cm from the SFJ or SPJ is an indication for HL/S rather than EVA.			
HL should not be added to patients being treated with EVA.	96%		
UGFS			
In the presence of C4-C6 disease in patients with reflux in a saphenous trunk >4 mm in diameter, UGFS is a treatment option.* †			93%
In the presence of C4-C6 disease in patients with reflux in a saphenous trunk <4 mm in diameter, UGFS is a valuable treatment option.*		80%	
In the presence of C4-C6 disease in patients with reflux in a saphenous trunk <4 mm in diameter and refluxing tributaries in a diseased skin area, UGFS of tributaries is preferred rather than phlebectomies.	+	87%	
In the presence of C4-C6 disease in patients with reflux in a saphenous trunk <4 mm in diameter and refluxing tributaries, UGFS and phlebectomies of tributaries at a distance from the diseased skin area, are both valuable treatment options.	+	92%	
In patients with venous symptoms and reflux in a saphenous trunk, UGFS (without tumescent anesthesia) is a valuable treatment option, even in the presence of a large (>10 mm) saphenous diameter.*		75%	
In patients with venous symptoms and reflux in a saphenous trunk vein >10 mm in diameter, where ablation is indicated, EVA is preferred rather than UGFS.	92%		
If you have decided to ablate the saphenous trunk, in the presence of C2-C3 disease in patients with venous symptoms and reflux in a saphenous trunk vein <4 mm in diameter, UGFS is preferred rather than EVA.* †			
EVA			
In the presence of C4-C6 disease in patients with reflux in a saphenous trunk <4 mm in diameter, EVA is a valuable treatment option.	+	71%	
ASVAL			
In the presence of C2-C3 disease in patients with venous symptoms, segmental reflux of a saphenous trunk <4 mm in diameter and large refluxing tributaries, preservation of the saphenous trunk is indicated rather than its ablation.* †			
ASVAL is not indicated in case of reflux in a saphenous trunk and C4-C6 disease.	83%		
Non-interventional measure			
In patients with venous symptoms, C2-C3 disease and reflux in a saphenous trunk and who are not willing to undergo any intervention or who are unfit for intervention because of extensive comorbidities, MECS should be considered.	88%		

Table 2. (continued)

Statements	Delphi rounds		
	1	2	3
In patients with venous symptoms, C2-C3 disease and reflux in a saphenous trunk and who are not willing to undergo any intervention or who are unfit for intervention because of extensive comorbidities, venotonic drugs should be considered.		79%	
In patients with C4-C6 disease and reflux in a saphenous trunk and who are not willing to undergo any intervention or who are unfit for intervention because of extensive comorbidities, MECS are indicated.	96%		
Comorbidities			
In patients with venous symptoms in addition to extensive comorbidities and reflux in a saphenous trunk, UGFS is indicated rather than EVA.*			
In patients with venous symptoms in addition to extensive comorbidities and reflux in a saphenous trunk, EVA or UGFS should only be considered in case of C4-C6 disease.*			
Morbid obesity			
In patients with venous symptoms, reflux in a saphenous trunk and morbid obesity, EVA or UGFS are indicated rather than HL/S.	87%		
In patients with venous symptoms, reflux in a saphenous trunk and morbid obesity, treatment should only be considered in case of C4-C6 disease.†			
In patients with venous symptoms, morbid obesity and reflux in a saphenous trunk, weight reduction is advized prior to any venous treatment.†	+		
Anticoagulation			
In patients with venous symptoms, reflux in a saphenous trunk and who are on chronic anticoagulants, EVA is indicated rather than HL/S.	92%		
In patients with venous symptoms, reflux in a saphenous trunk <4 mm diameter and who are on chronic anticoagulants, UGFS is indicated rather than HL/S.*		91%	
In patients with venous symptoms, reflux in a saphenous trunk and who are on chronic anticoagulants, EVA can be performed without bridging.	87%		
In patients with venous symptoms, reflux in a saphenous trunk and who are on chronic anticoagulants, UGFS can be performed without bridging.	88%		
In patients with venous symptoms, who are on chronic anticoagulants and who are scheduled for extensive phlebectomies, temporary discontinuation or anticoagulant treatment bridging is indicated.†			88%
Severe peripheral arterial disease			
In patients with C2-C3 disease, reflux in a saphenous trunk and severe peripheral arterial disease, it is preferable not to ablate the saphenous vein by means of EVA, UGFS or HL/S.	79%		
In patients with C4-C6 disease, reflux in a saphenous trunk and severe peripheral arterial disease, EVA or UGFS of the refluxing saphenous vein may be considered.	71%		

Consensus on agreeing with the statement
Consensus on disagreeing with the statement
Equivocal (no complete agreement nor disagreement)

* Statement was reformulated after first round. † Statement was reformulated after second round. + Statement was added after remarks of experts in the first round.

Abbreviations: EVA, endovenous ablation (including thermal and non-thermal non-tumescent techniques, excluding UGFS), HL/S, high ligation with stripping; SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; UGFS, ultrasound-guided foam sclerotherapy; ASVAL, 'ambulatory selective varicose ablation under local anesthesia' (= single phlebectomies without treating the saphenous trunk); MECS, medical elastic compression stockings.

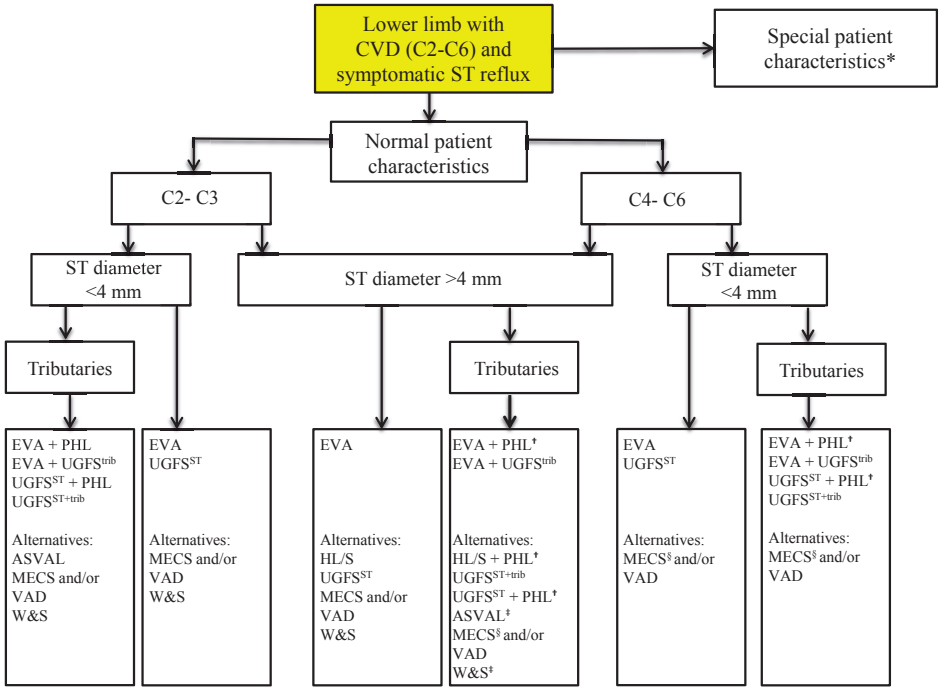

Figure 3. Flowchart of management strategies in patients with chronic venous disease (C2-C6) and symptomatic saphenous trunk reflux

† Special patients characteristics includes: extensive comorbidities, severe peripheral arterial disease (ankle brachial index <0.6) and/or patients under chronic anticoagulant treatment. ‡ In patients with C4-C6, only phlebectomies away from area of diseased skin. * Only in limbs with C2-C3. § In patients with C6 use alternative compression (short stretch bandage or Velcro).

Abbreviations: CVD, chronic venous disease; ST, saphenous trunk; trib, tributaries ASVAL, ambulatory selective varices ablation under local anesthesia of tributaries; UGFS, ultrasound-guided foam sclerotherapy; PHL, phlebectomies of tributaries; MECS, medical elastic compression stockings; VAD, veno-active drugs; W&S, wait and see; EVA, endovenous thermal or non-thermal ablation of trunk; HL/S, high ligation and stripping.

which may help physicians to make supported and personalized choices for their patients with CVD (C2-C6).

Not surprisingly, experts' recommendations regarding EVA were in line with current guidelines on the care of patients with varicose veins and associated CVD.[5-8] EVA was considered the preferred treatment for most symptomatic patients with CVD (C2-C6) and a refluxing ST >4 mm in diameter. The expert panel did not recommend an alternative treatment for specific DUS findings such as terminal valve reflux, a large (>10 mm) ST diameter or presence of one or more focal dilatations of the ST (Table 2). EVA has now globally become the preferred treatment for ST reflux as is reflected in the flowchart. Although EVA has largely replaced HL/S, it should be acknowledged that, whenever

equipment for EVA is not available, HL/S (ideally applying under tumescent anesthesia) is a valuable treatment option. While the patient reported outcomes favor EVTA, long-term efficacy of HL/S is similar to EVTA.[15,16]

UGFS is usually considered the second best option of the minimally invasive treatments for treating ST reflux.[5-8] In the present consensus approach, the experts considered UGFS to be just 'a' treatment option if ST diameter is ≥4 mm, and only agreed on categorizing it 'a valuable treatment option' for STs with small diameters <4 mm. This discrepancy illustrates that ST diameter may be used as a relevant criterion to distinguish between different treatment options,[1] which is in line with the European guidelines for sclerotherapy.[17]

At the end of the first round of the Delphi consensus, older age appeared to be less relevant than we initially had hypothesized and it was therefore converted into extensive comorbidities as suggested by the participants from the second round onwards. Indeed, clinical studies demonstrated that the feasibility and safety of EVTA and tolerability of UGFS were similar in patients older and younger than 75 years of age.[18,19] In contrast, studies regarding venous treatments in patients with (extensive) comorbidities are lacking. Although the investigators thought that minimizing the extent of procedures in patients with comorbidities and/or morbid obesity would be good clinical practice, experts did not reach consensus on this issue. This lack of consensus could in part be explained by the fact that many different combinations of comorbidities can be thought of in these cases. Therefore, these patients definitely belong to the group of patient with 'specific patient characteristics' for which no detailed management strategy could be mentioned in the flowchart. Also, patients under chronic anticoagulant treatment and those with severe peripheral arterial disease belong to this more exceptional patient group, but the experts seemed to be more unanimous regarding strategies in the latter two groups of patients.

ASVAL is not yet a worldwide-accepted strategy, and this was reflected in the Delphi consensus. Contrarily to what the investigators had been suggesting, the experts could not agree on particular criteria for implementing ASVAL so far. This is somehow to be expected as only 42% of the experts had ever used ASVAL in their clinical practice (data not shown) and the evidence on the subject is still limited.[11,20,21]

In the present study we proposed a flowchart that may be used in clinical practice for defining the best treatment strategy in patients with CVD. Of course physicians should also consider patient's preference, as well as the impact of the disease on Health-Related Quality of Life (HRQoL), the estimated risk of deterioration of CVD and local health care resources. Although the flowchart represents a well-defined strategy for lower limbs with varicose veins and associated CVD, the position of ASVAL still remains indefinite, but this may change in the future. Therefore, the proposed flowchart should be considered as a dynamic tool, to be updated as soon as results of future studies become available.

Limitations

This study has several limitations. The statements may have been incomplete, but this was minimized because they were based on a prior worldwide survey among 211 specialists in CVD.[5] Selection bias among the eligible experts might have occurred, but we tried to invite a heterogeneous group of physicians and the response rate was almost perfect. In the absence of clear guidelines, we chose the cut-off value of 70% as acceptable, because of the relatively mild impact of CVD on HRQoL, contrarily to decision making in more life-threatening diseases in which a higher cut-off may be desired. In addition, there is no standard method for calculating sample sizes for a Delphi study, but there is evidence that expert panels of 20 can reach a valid consensus.[22]

Conclusion

In conclusion, we propose recommendations, which can be used in the majority of CVD patients to further optimize phlebologic care for individual patients.

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SUPPLEMENTARY

Supplementary Table 1. Adapted and removed statements

Adapted statements[§]:

1. In case of reflux in saphenous trunk, UGFS is a valuable treatment option, even in the presence of C4-C6 disease.
   - In the presence of C4-C6 disease in patients with reflux in a saphenous trunk **>4 mm** in diameter, UGFS is a valuable treatment option.[*]
   - In the presence of C4-C6 disease in patients with reflux in a saphenous trunk **>4 mm** in diameter, UGFS is a ~~**valuable**~~ treatment option.[†]
   - In the presence of C4-C6 disease in patients with reflux in a saphenous trunk **<4 mm** in diameter, UGFS is a valuable treatment option.[*]
2. In patients with venous symptoms and reflux in a saphenous trunk >10 mm in diameter, where ablation is indicated, EVA is preferred rather than UGFS.
   - In patients with venous symptoms and reflux in a saphenous trunk, **UGFS (without tumescent anesthesia) is a valuable treatment option,** even in the presence of a large (>10 mm) saphenous diameter.[*]
3. In patients with venous symptoms and reflux in a saphenous trunk vein <4 mm in diameter, where ablation is indicated, UGFS is preferred rather than EVA.
   - **In the presence of C2-C3 disease** in patients with venous symptoms and reflux in a saphenous trunk <4 mm in diameter, where ablation is indicated, UGFS is preferred rather than EVA.[*]
   - **If you have decided to ablate the saphenous trunk**, in the presence of C2-C3 disease in patients with venous symptoms and reflux in a saphenous trunk vein <4 mm in diameter, UGFS is preferred rather than EVA.[†]
4. In most patients with venous symptoms, reflux in a saphenous trunk <4 mm in diameter and refluxing tributaries, preservation of the saphenous trunk is indicated rather than its ablation
   - **In the presence of C2- C3 disease in patients with** venous symptoms, reflux in a saphenous trunk <4 mm in diameter and refluxing tributaries, preservation of the saphenous trunk is indicated rather than its ablation.[*]
   - In the presence of C2- C3 disease in patients with venous symptoms, **segmental reflux of a saphenous trunk** <4 mm in diameter and **large** refluxing tributaries, preservation of the saphenous trunk is indicated rather than its ablation.[†]
5. In patients aged >80 yrs with venous symptoms and reflux in a saphenous trunk, UGFS is indicated rather than EVA.
   - In patients with venous symptoms **in addition to extensive comorbidities** and reflux in a saphenous trunk, UGFS is indicated rather than EVA.[*]
6. In patients aged >80 yrs, with venous symptoms and reflux in a saphenous trunk, EVA or UGFS should only be considered in case of C4-C6 disease.
   - In patients with venous symptoms **in addition to extensive comorbidities** and reflux in a saphenous trunk, EVA or UGFS should only be considered in case of C4-C6 disease.[*]
7. In patients with venous symptoms, reflux in a saphenous trunk and morbid obesity, EVA or UGFS should only be considered in case of C4-C6 disease.
   - In patients with venous symptoms, reflux in a saphenous trunk and morbid obesity, **treatment** should only be considered in case of C4-C6 disease.[†]
8. In patients with venous symptoms, morbid obesity and reflux in a saphenous trunk, weight reduction is recommended prior to any venous treatment.

- In patients with venous symptoms, morbid obesity and reflux in a saphenous trunk, weight reduction is **advized** prior to any venous treatment.†

9 In patients with venous symptoms, reflux in a saphenous trunk and who are on chronic anticoagulants, UGFS is indicated rather than HL/S.

- In patients with venous symptoms, reflux in a saphenous trunk **<4 mm diameter** and who are on chronic anticoagulants, UGFS is indicated rather than HL/S.*

10. In patients with venous symptoms, who are on chronic anticoagulants and who are scheduled for extensive phlebectomies, bridging is indicated.

- In patients with venous symptoms, who are on chronic anticoagulants and who are scheduled for extensive phlebectomies, **temporary discontinuation of anticoagulant treatment** or bridging is indicated.†

§ Adaptions are described in red. * Statement was reformulated after first round. † Statement was reformulated after second round.

Removed statements:

1. In patients with venous symptoms and reflux in a saphenous trunk UGFS is a valuable treatment option, even in the presence of TV reflux (after first round).
2. In patients with venous symptoms, clinically relevant varicose veins (C2-C3 disease), reflux in a saphenous trunk and refluxing tributaries, ASVAL is a valuable treatment option (after second round).
3. In patients with venous symptoms, clinically relevant varicose veins (C2-C3 disease) and refluxing tributaries, ASVAL is indicated only in case of segmental reflux in a saphenous trunk (after second round).

CHAPTER 7

General discussion

BACK TO BASICS: THE PATHOPHYSIOLOGY OF SUPERFICIAL VENOUS INCOMPETENCE IN CHRONIC VENOUS DISEASE

For many years reflux has been explained according to the 'descending' pathophysiologic concept, stating that superficial venous reflux starts with valvular incompetence at the level of a junction between the deep and superficial system and further progresses downwards from the saphenous trunk (ST) to the tributaries. At that time, treatment mainly aimed at abolition of reflux especially at the junction and therefore systematic high ligation at the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ) was considered an essential part of the gold standard treatment.[1] Over the past decades, our knowledge about the pathophysiology of chronic venous disease (CVD) has grown considerably. The experience with endovenous thermal and non-thermal ablation techniques as well as ultrasound-guided foam sclerotherapy (UGFS) - has taught us that a refluxing ST can be efficaciously treated without ligation of the SFJ or SPJ. In addition, several studies have provided evidence for the existence of a multifocal or ascending theory, which states that reflux starts at the level of tributaries and further ascends towards the ST and junctions.[2-5] The presence of microvalves has been illustrated by Vincent et al. using electron microscopy. They showed that valvular reflux can exist in the very small superficial veins of the leg independently of incompetence in the great saphenous vein (GSV) or its tributaries.[6] This new 'ascending' concept supports the idea of treating patients with minimally invasive methods such as isolated phlebectomies without treatment of the ST, called 'ASVAL' (Ambulatory Selective Varices Ablation under Local anesthesia).[7] The ASVAL strategy has been launched by Pittaluga and colleagues[7], who suggested that competence of a refluxing ST can be restored by removing refluxing tributaries only. In a retrospective study of 303 limbs with varicose veins and ST reflux treated by means of ASVAL, they reported successful abolition of reflux in 66% of limbs.[8] Nowadays, understanding the pathophysiology of CVD in an individual patient - whether ascending, descending or a combination of both- has become of utmost importance for phlebologic specialists and this should definitely be integrated in their daily routine treatment considerations.

If reflux in a ST is a potentially reversible phenomenon, as described above, this must be somehow related to the biophysical properties of the vein wall, which was studied in **chapter 4**. In the first part of this chapter, we hypothesized that severity of CVD may correlate with some of the vein wall properties such as elasticity, which is a term of physics describing the 'continuum mechanics of bodies that deform reversibly under stress'. Elasticity of the ST was measured by means of duplex ultrasound (DUS) in standing and lying position to calculate the postural diameter change (PDC) of the ST. Similar work has been performed by Jeanneret et al.[9] However they focused on distensibility of the venous wall, which is another biophysical property. The latter is defined as 'the ability to

become stretched, dilated or enlarged'. In patients with varicose veins, distensibility of the GSV was positively related to flow volume, peak reflux velocity, absolute displaced volume and time average mean velocity.[9] In addition, patients with varicose veins had significantly higher venous distensiblity than healthy controls.[10] Interestingly, focusing on elasticity of the vein wall, we observed a trend towards a lower PDC (and hence less elasticity) in limbs with more advanced stages of CVD. Whether PDC may be used as an additional tool to stratify limbs with CVD should be further investigated and the effect of the morphology of the venous wall on PDC should be studied in detail.

In the second part of **chapter 4** we showed that focal dilatations were independently associated with presence of junctional reflux and a large saphenous diameter. These findings were similar to the results of Labropoulos et al.[11] In their large prospective study, presence of focal dilatations was significantly less frequent in limbs with C2-C3 disease than in limbs with C4-C6 disease.[11] Unfortunately, we were unable to confirm their results because our study population had predominantly less advanced stages of CVD (C2-C3).

Chronic venous hypertension may cause localized weakness of the venous walls and subsequently focal venous dilatations increase in size and number. Our results may contribute to a better understanding of the pathophysiology related to superficial venous incompetence in patients suffering from CVD. Also, presence of one or more focal dilatations may be used as an additional tool to measure disease severity, in particular within the large group of limbs with C2-C3 disease. For example, presence of focal dilatations may suggest the disease already has more hemodynamic impact and therefore a more invasive treatment strategy may be preferred.

CHRONIC VENOUS DISEASE: A NEVER-ENDING STORY

The chronic character of CVD and the risk of developing recurrence after a previous intervention emphasize the need for long-term follow-up of patients included in clinical trials. Long-term follow-up studies not only evaluate the efficacy of the different management strategies but also provide more insight in progression of venous disease over time. All this knowledge should be taken on board when making decisions for an individual patient in clinical practice.

Although conventional surgery (CS), consisting of high ligation and stripping, usually combined with phlebectomies, and endovenous laser ablation (EVLA) were more effective than UGFS for the treatment of GSV reflux, there was no difference in recurrence of varicose veins after five years follow-up (**chapter 3**). This seems to suggest that the extent of disease progression is independent of the type of treatment. Interestingly, CS – preferably performed under local tumescent anesthesia - still appears to be a good al-

ternative therapeutic option, although worldwide it is now increasingly being replaced by endovenous treatment techniques.

In the past year, several long-term results of randomized controlled trials (RCTs) comparing EVLA with CS have been published and more long-term high-quality evidence is still to be awaited.[12-14] It would be interesting to conduct a comprehensive systematic review comparing the long-term outcomes of CS, endovenous thermal ablation (EVTA) and UGFS. Ideally, this review should identify predictors for recurrence and/or disease progression in patients treated with either CS, EVTA or UGFS. In **chapter 5**, we already took the first step towards identifying predictors for recanalization of the GSV 1 year after treatment with EVTA. Our findings may prove valuable assets in clinical practice because the identification of these predictors will result in optimization of the treatment of patients with CVD, allowing a more personalized approach.

TOWARDS A MORE PERSONALIZED MEDICINE: IMPLICATIONS FOR PATIENTS WITH CHRONIC VENOUS DISEASE

Although the decision to treat a patient is usually based on different elements (e.g., symptoms, patient preference, clinical signs, hemodynamic status according to DUS), it most likely depends on the presence of venous symptoms or clinical signs of more advanced CVD, such as edema and skin changes. In the past, offering treatment to patients with non-specific symptoms might have contributed to overtreatment and disappointing outcomes in terms of patients' satisfaction. In a large British registry, almost 89% of patients undergoing hip surgery and 81% of patients undergoing knee surgery reported an improvement in general health after the operation, whereas only 54% of varicose vein patients showed improvement.[15] However, if disease-specific questions were recorded, improvement rate increased to 84% after varicose vein surgery compared to 97% and 94% after hip and knee surgery respectively.[15] In addition, one prospective study showed that some symptoms resolved completely after treatment whereas others persisted to a lesser or greater degree.[16] According to our findings in **chapter 2**, venous symptoms are not pathognomonic for CVD but may be suggestive of CVD, particularly if they are more pronounced at the end of the day. In some patients, the origin of symptoms remains uncertain: even after taking a complete medical history and performing a thorough clinical and DUS examination, there may still be doubts whether the symptoms are really 'venous'. In these cases, it should be clearly discussed with the patient that outcome of whatever venous intervention is uncertain, and may even be very disappointing. Importantly, symptoms alone without proof of venous pathology according to DUS do not justify the initiation of any treatment other than conservative measures (e.g., medical elastic compression stockings [MECS]).[17]

Individualized care results in different treatment strategies, adapted to each patient with CVD. Depending on patient's characteristics and DUS findings, this may either lead to a less invasive or more invasive approach. Hence, care should be taken to provide correct patient education to avoid any confusion or misunderstanding. Patients tend to exchange their experiences, and may wonder why they don't get the same treatment as their neighbor. Decision making should therefore be a process shared between patient and physician and this can be facilitated by providing decision tools that raise patients' awareness and understanding of treatment options and possible outcomes.[18] Decision tools can efficiently help patients absorb relevant clinical evidence and aid them in developing and communicating informed preferences.[15] Unfortunately, there are no shared-decision tools available in phlebology yet. The proposed flowchart in **chapter 6** – up to now made for physicians only - may be considered a first step towards more shared-decision care in the future. For example, the flowchart illustrates that UGFS is more 'valuable' in small diameter ST than in large diameter trunks. This can easily be explained to an individual patient, who will understand much more easily why one or the other treatment is the preferred option. Obviously, the flowchart needs to be adapted using patients' language to increase interpretability.

TOWARDS MORE PERSONALIZED MEDICINE: IMPLICATIONS FOR CLINICAL PRACTICE

In an era of increasing health care costs, with procedure driven reimbursement, more efficient treatment of patients with varicose veins is warranted. Targeted treatment may not only improve patient-centered health care but may also reduce the burden of treatment costs for the society, by avoiding unnecessary procedures resulting in less treatment-related complications and a faster postoperative recovery. Physicians should recognise these advantages and implement individualized care in clinical practice. This implies that simply obeying the recommendations of the phlebologic guidelines is no longer sufficient. Criteria for venous treatment should shift from presence of ST reflux only[19] to a combination of patient characteristics, clinical and DUS findings.[7,20] This means alternative treatments should be considered such as UGFS and ASVAL, instead of always obstinately ablating the refluxing ST with one of the, definitely more expensive, thermal or non-thermal ablation techniques. Minimally invasive medicine is especially indicated in patients with extensive comorbidities.[21] We summarized several criteria and treatment strategies in a flowchart for management of patients with CVD and superficial venous reflux (**chapter 6**). The flowchart may assist physicians to optimize their management decisions. It is obvious that the proposed flowchart includes many management alternatives, which enable physicians to choose a strategy that is not only optimal for

the individual patient, but is also the most feasible in view of their own experience and current setting. Clearly, when using this flowchart, physicians should always adhere to 'good clinical practice' considering patient preferences, Health-Related Quality of Life, estimated risk of deterioration of CVD, reimbursement criteria, and local health care resources.

In July 2014, Dutch reimbursement criteria for treating patients with CVD were sharpened because of the increasing health care expenses. Only symptomatic patients with a refluxing junction and a ST ≥ 3 mm in diameter can receive reimbursement for their varicose vein treatment.[22] While most insurance companies only cover EVTA treatment (and recently mechanochemical ablation with Clarivein®), only a few also allow treatment with UGFS and ASVAL. This inconsistency and the frequent adjustment of reimbursement criteria are frustrating practitioners and patients alike. Many patients do not fit in the above-described criteria (e.g., patients with extensive recurrent varicose veins, without clearly refluxing junction) and definitely would need a patient-tailored intervention. On the other hand, other patients nowadays still undergo unnecessary treatments, based on the fact that they fit in the same criteria. This is absolutely not logical neither cost-effective.

In general, costs have unfortunately not been reduced by the current reimbursement restrictions and therefore we are convinced national health care should open up for new ideas. Personalized medicine will not only improve the quality of healthcare and assist in disease prevention, but may also lead to lowering health care costs.[25] The ability to predict which patient will benefit from a given treatment and which patient is likely to suffer from important adverse effects could result in meaningful cost savings for the overall health care system.[24] Therefore, if the Dutch National Health Care Institute (ZiN), formerly named Health Care Insurance Board (CVZ), would agree with our proposed flowchart, treatment could be offered to all patients presenting with venous symptoms and reflux of the ST who need treatment. In such case, EVTA (or a non-thermal ablation technique) could be replaced by one of the cheaper alternatives (e.g., UGFS, ASVAL or even MECS) in well-defined patients.

Recently, several initiatives have been set-up to encourage affordable care. For example, The Netherlands Organisation for Health Research and Development has started Health Care Efficiency Research programs to fund new studies focussing on efficiency in health care.[26] In the context of this program, we have set-up a RCT comparing Single Ambulatory Phlebectomies (SAP) with the combination of Thermal Ablation (EVLA) and concomitant Phlebectomies (TAP) in patients with a refluxing GSV or anterior accessory saphenous vein and at least one important refluxing varicose tributary. The aim of this RCT is to test whether the conservative and less invasive strategy (SAP), which is the cheaper option, is as effective as TAP. The collected data will also be used to develop a prediction model identifying the patients who most likely could benefit from this more

conservative ST-sparing approach. We are convinced that more initiatives focussing on cost-effective treatments are needed to keep phlebologic care affordable for the future generation.

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CHAPTER 8

Summary / samenvatting

SUMMARY

Chapter 1 contains a general introduction to this thesis. Over the past two decades, many long-term prospective studies and randomized controlled trials (RCTs) have established evidence-based medicine (EBM) in phlebology. In a short period of time, several effective minimally invasive treatment possibilities have become available, which may accommodate practitioners to a more personalized treatment. The algorithm I proposed may help practitioners in their decisions on treatment strategies for patients with chronic venous disease (CVD), optimizing personalized medicine. In this thesis I aimed to investigate factors that may influence management decisions. Also I evaluated the specificity of venous symptoms, long-term effects of venous treatments and patient-specific predictors of treatment outcomes. In addition, I assessed the biophysical properties of the saphenous trunk (ST). These outcomes may all help in clinical decision-making.

In **chapter 2** we first translated the English VEINES-QOL/Sym questionnaire into Dutch. In 66 patients with CVD, the Dutch VEINES-QOL/SYM was subsequently tested for psychometric properties and validated with the SF-36 questionnaire. The Dutch VEINES-QOL/SYM showed a good acceptability, validity and high reliability and was therefore used in our second study. In the second part of **chapter 2**, we used the Dutch VEINES-SYM questionnaire to compare the frequency of venous symptoms between 76 patients with CVD and venous reflux and 74 patients with other diseases of the legs (e.g., arthrosis, peripheral arterial disease and spinal disc herniation) without venous reflux. Although presence of venous symptoms was slightly more often reported in the CVD group than in the other group, differences were small and statistically non-significant. The largest difference between the CVD and 'other' group was observed for the time of the day at which symptoms were most intense: patients with CVD were more likely to experience symptoms at the end of the day ($p < .001$). This may imply that venous symptoms are less specific for CVD than is usually assumed.

In **chapter 3** we evaluated the long-term effectiveness of conventional surgery (CS), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for primary great saphenous vein (GSV) reflux. We treated 224 legs (69 CS 78 EVLA, 77 UGFS), of which 86.2% were evaluated at 5-year follow-up. At 5 years, Kaplan–Meier estimates of obliteration or absence of the GSV were 85%, 77% and 23% in the CS, EVLA, and UGFS group respectively. CIVIQ scores deteriorated over time in the UGFS group (0.98 increase per year), and were significantly worse than those in the EVLA group (−0.44 decrease per year, $p = .013$). CIVIQ scores for the CS group did not differ from those in the EVLA and UGFS groups (0.44 increase per year). EQ-5D™ scores improved equally in all groups. This shows that CS and EVLA are more durable than UGFS in obliterating the GSV

five years after treatment for GSV reflux. UGFS was associated with significantly inferior CIVIQ scores compared with EVLA.

In **chapter 4** we focused on the biophysical properties of the saphenous trunk. In the first part we investigated the correlation between the postural diameter change (PDC) of the saphenous trunk (ST) and patient and/or duplex ultrasound (DUS) characteristics. We measured the inner diameter of the ST in standing and in lying positions in 193 legs with and 48 legs without saphenous trunk (ST) reflux. Legs were divided into two groups using the median value of PDC as a cut-off to increase interpretability of the analysis. In legs with and without ST reflux, age >65 years and body mass index (BMI) >30 kg/m^2 were correlated with a less than median PDC In the second part of **chapter 4** we assessed the distribution of focal dilatations and associated factors in 193 limbs with ST reflux from the previous study. One or more focal dilatations were found in 68 STs (35%), in either the great saphenous, small saphenous or anterior accessory saphenous vein. The median diameter of the ST and presence of junctional reflux were independently associated with the presence of one or more focal dilatations. The latter finding illustrates the correlation between presence of one or more focal dilatations and more advanced stages of CVD.

In **chapter 5** we first searched for predictors of recanalization of the GSV and change of Health-Related Quality of life (ΔHRQoL) in 1226 legs treated with endovenous thermal ablation (EVTA) using data from 15 RCTs. Second, we developed and validated the models (e.g., GSV recanalization and ΔHRQoL model). At 1 year follow-up, 130 GSVs had recanalized (11%). The strongest predictors of recanalization were clinical class (C of the CEAP classification) (Odds Ratio [OR] 2.1) and GSV diameter (OR 1.8). The performance of the recanalization model was moderate (Area Under the Curve 0.717). GSV diameter, type of device and delivered amount of energy were the only predictors for ΔHRQoL but none of these candidate predictors were included in the final ΔHRQoL model (R^2 of 0.03). This is the first study demonstrating that several predictors are involved in the etiology of GSV recanalization and ΔHRQoL.

In **chapter 6** we focused on personalized medicine in patients with CVD. First, the influence of patient characteristics and DUS findings on management decisions was investigated in a worldwide group of 211 physicians with a specific interest in the field of CVD. An online survey was used to distribute different clinical scenarios about strategies in patients with reflux of the GSV and tributaries. The majority of physicians would adapt their strategy in case of older age (61%), peripheral arterial disease (64%), and body mass index (BMI) >40kg/m^2 (52%). Also, 74% of the respondents answered that vein diameter was important for their treatment strategy. The results of this study were pro-

cessed in the second part of **chapter 6**, in which we used a Delphi methodology. Over the course of three consecutive rounds we tried to reach consensus about management criteria for symptomatic patients with CVD (C2-C6) and superficial vein reflux. Considerable consensus was reached in 25 out of 32 statements (78%) addressing criteria for endovenous ablation, UGFS, high ligation and stripping, single phlebectomies and non-interventional measures within a group of 24 experts. Also, a flowchart was developed based on the findings of the Delphi consensus. These studies are the first step toward a more personalized treatment of patients with CVD.

In **chapter 7** we discussed the different factors influencing management strategies in patients with CVD. We stated that understanding the pathophysiology of CVD is very important when defining management strategies. Also, knowledge about progression of venous disease seems relevant when making decisions for an individual patient. Furthermore, we discussed the implications of personalized medicine for patients with CVD in daily phlebologic practice. The discussion ended by advocating that more research focussing on cost-effective treatments is needed to keep phlebologic care affordable for the future generation.

SAMENVATTING

Hoofdstuk 1 geeft een algemene introductie van dit proefschrift. In de afgelopen twintig jaar hebben vele langdurige prospectieve en gerandomiseerde studies een grote bijdrage geleverd aan de wetenschappelijke bewijsvoering binnen de flebologie. In een korte periode zijn er meerdere minimaal invasieve behandelingsopties op de markt gekomen. Door de toename van opties is het nu voor de arts mogelijk geworden om de behandeling meer aan te passen aan de individuele patiënt. Het algoritme, dat ik in dit proefschrift voorstel, kan artsen helpen in het maken van een keuze in de behandeling van patiënten met chronische veneuze ziekte. In dit proefschrift onderzoek ik factoren die mogelijk een invloed hebben op deze keuzes. Ook kijk ik naar de specificiteit van veneuze symptomen, langetermijnresultaten van veneuze behandelingen en patiënt specifieke voorspellers van behandelingsresultaten. Daarnaast onderzoek ik de biofysische eigenschappen van de stamvenen. Alle (boven)genoemde uitkomsten kunnen mogelijk helpen in het maken van klinische behandelkeuzes.

In **hoofdstuk 2** hebben we allereerst de VEINES-QOL/Sym vragenlijst vanuit het Engels vertaald naar het Nederlands. Vervolgens werden de psychometrische eigenschappen van de Nederlandse versie bij 66 patiënten met chronische veneuze ziekte getest en gevalideerd met de SF-36 vragenlijst. De Nederlandse versie toonde een goede acceptatie, validiteit en hoge betrouwbaarheid en kon daardoor worden gebruikt in onze tweede studie. In het tweede deel van **hoofdstuk 2** werd de Nederlandse VEINES-QOL/Sym gebruikt om de frequentie van veneuze symptomen te vergelijken tussen 76 patiënten met chronische veneuze ziekte en reflux in het veneuze systeem enerzijds en 74 patiënten met andere aandoeningen van het been (bv. artrose, perifeer arterieel vaatlijden en lumbale hernia) maar zonder reflux. Ondanks dat veneuze symptomen iets vaker aanwezig waren in de chronische veneuze ziekte groep dan in de andere groep, waren de verschillen klein en niet-significant. Het grootste verschil tussen de groepen werd gevonden betreffende het tijdstip van de dag waarop de symptomen het meest intensief zijn: patiënten met chronische veneuze ziekte hadden vaker symptomen aan het einde van de dag ($p < .001$). Dit zou kunnen betekenen dat veneuze symptomen minder specifiek zijn voor chronische veneuze ziekte dan voorheen werd aangenomen.

In **hoofdstuk 3** hebben we de langetermijnresultaten van crossectomie met strippen vergeleken met endoveneuze laser ablatie (EVLA) en echogeleide foamsclerose therapie (ESCT) voor de behandeling van vena saphena magna (VSM) reflux. Er werden voor deze studie 224 benen behandeld (69 crossectomie met strippen, 78 EVLA, 77 ESCT) waarvan er 86% werden geëvalueerd gedurende 5 opeenvolgende jaren. Na 5 jaar had respectievelijk 85%, 77% en 23% in de crossectomie met strippen, EVLA en ESCT groep

een geoblitereerde of afwezige VSM volgens de Kaplan-Meier schatting. De CIVIQ scores verslechterden over de tijd in de ESCT groep (0.98 toename per jaar) en deze waren significant slechter dan in de EVLA groep (−0.44 afname per jaar, p = .013). De CIVIQ scores in de crossectomie met strippen groep waren vergelijkbaar met die van de EVLA en ESCT groep (0.44 toename per jaar). De EQ-5D™ scores verbeterden op hetzelfde niveau in alle groepen. Deze bevindingen laten zien dat crossectomie met strippen en EVLA betere langetermijnresultaten hebben dan ESCT wat betreft het oblitereren/verwijderen van de VSM 5 jaar na behandeling voor VSM reflux. ESCT was geassocieerd met significant slechtere CIVIQ scores vergeleken met EVLA.

In **hoofdstuk 4** hebben we ons gericht op de biofysische eigenschappen van de stamvenen. In het eerste gedeelte onderzochten we de correlatie tussen de positionele diameter verandering (PDV) van de stamvenen en patiënt en/of duplex kenmerken. De binnenste diameter van de stamvene werd gemeten in zowel staande als liggende houding in 193 benen met, en 48 zonder reflux van de stamvene. De benen werden verdeeld in twee groepen waarbij de mediane waarde van de PDV werd gebruikt als afkapwaarde om zo de interpretatie van de analyse te verduidelijken. Leeftijd boven de 65 jaar en body mass index (BMI) hoger dan 30 kg/m^2 waren gecorreleerd met een grotere PDV dan de mediaan in benen met en zonder reflux van de stamvene. In het tweede deel van **hoofdstuk 4** bepaalden we in de 193 benen met reflux van de stamvene uit de voorgaande studie, de verdeling van focale dilataties en factoren die hiermee geassocieerd zijn. In 68 stamvenen (35%) van de VSM, vena saphena parva of vena saphena accessoria anterior werden één of meer focale dilataties gevonden. De mediane diameter van de stamvene en aanwezigheid van crosse reflux waren onafhankelijk geassocieerd met de aanwezigheid van één of meerdere focale dilataties. Dit laatste bevestigt een correlatie tussen de aanwezigheid van een of meerdere focale dilataties en gevorderde chronische veneuze ziekte.

In **hoofdstuk 5** zochten we eerst naar voorspellende factoren voor rekanalisatie van de VSM en veranderingen (Δ) in kwaliteit van leven op het gebied van gezondheid in 1126 benen die behandeld werden met endoveneuze thermische ablatie (EVTA). Hiervoor werden de data van 15 gerandomiseerde en gecontroleerde studies gebruikt. Daaropvolgend werden er twee modellen ontwikkeld en gevalideerd (VSM rekanalisatie en Δ kwaliteit van leven model). Na 1 jaar waren er 130 VSM's gerekanaliseerd (11%). De sterkste voorspellende factoren voor rekanalisatie waren klinische klasse (C van de CEAP classificatie) (Odds Ratio [OR] 2.1) en VSM diameter (OR 1.8). De betrouwbaarheid van het rekanalisatiemodel was middelmatig (Area Under the Curve, of oppervlakte onder de lijn, 0.717). VSM diameter, type apparaat gebruikt voor de EVTA en totaal geleverde energie waren de enige voorspellende factoren voor Δ kwaliteit van leven, echter, geen

van deze kandidaat-voorspellende factoren werd geïncludeerd in het uiteindelijke Δ kwaliteit van leven model (R^2 van 0.027). Dit is de eerste studie die aantoont dat verschillende voorspellende factoren zijn betrokken bij de etiologie van VSM rekanalisatie en Δ kwaliteit van leven.

In **hoofdstuk 6** hebben we ons gericht op een individuele aanpak bij patiënten met chronische veneuze ziekte. In het eerste gedeelte van hoofdstuk 6 werd de invloed van patiëntgebonden eigenschappen en duplexbevindingen op het kiezen van een behandeling onderzocht in een groep met 211 artsen, die een specifieke interesse hebben in chronische veneuze ziekte. Met behulp van een digitale vragenlijst werden er verschillende klinische scenario's over behandelingsstrategieën bij patiënten met reflux van de VSM en zijtakken voorgesteld. Het merendeel van de artsen pasten hun behandelingsstrategie aan in geval van een hogere leeftijd (61%), perifeer arterieel vaatlijden (64%) en BMI >40kg/m^2 (52%). Ook gaf 74% van de respondenten aan dat de diameter van de vene een belangrijke rol speelt in het kiezen van een behandeling. De resultaten van deze studie werden verwerkt in het tweede deel van hoofdstuk 6, waarbij we een Delphi methode toepasten. In drie opeenvolgende rondes werd gepoogd zoveel mogelijk overeenstemming te bereiken over behandelingscriteria voor symptomatische patiënten met chronische veneuze ziekte (C2-C6) en oppervlakkige veneuze reflux. In een groep van 24 experts, werd een aanzienlijke consensus bereikt over 25 van de 32 stellingen (78%) met betrekking tot criteria omtrent endoveneuze ablatie, ESCT, crossectomie met strippen, alléén ambulante flebectomie en conservatieve behandelingen. Daarnaast werd er, gebaseerd op de bevindingen van de Delphi consensus, een flowchart ontwikkeld. Deze beide studies zijn een eerste stap richting een meer individuele behandeling van patiënten met chronische veneuze ziekte.

In **hoofdstuk 7** bediscussieerden we de verschillende factoren die een invloed hebben op de behandelingsstrategieën bij patiënten met chronische veneuze ziekte. We benadrukten dat het belangrijk is de pathofysiologie bij chronische veneuze ziekte te begrijpen om de juiste behandelbeslissingen te kunnen nemen. Kennis over progressie van de ziekte is ook van belang in het maken van beslissingen voor de individuele patiënt. We bediscussieerden daarnaast de betekenis van een individuele aanpak bij patiënten met chronische veneuze ziekte voor de flebologische praktijk. De discussie eindigt met de stelling dat er meer onderzoek nodig is naar kosten effectieve behandelingen die de flebologische zorg betaalbaar kunnen houden voor toekomstige generaties.

CHAPTER 9

Appendices

Abbreviations

List of Co-authors

List of Publications

Curriculum Vitae

PhD Portfolio

Acknowledgments/Dankwoord

ABBREVIATIONS

AASV	Anterior Accessory Saphenous Vein
ABI	Ankle Brachial Index
AP	Ambulatory Phlebectomy
ASVAL	Ambulatory Selective Varices Ablation under Local anesthesia
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	Body Mass Index
CEAP	Clinical Etiologic Anatomic Pathophysiologic classification
CHIVA	Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire
CI	Confidence Interval
CIVIQ	Chronic Lower Limb Venous Insufficiency
CS	Conventional Surgery
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
DUS	Duplex UltraSound
DVT	Deep Vein Thrombosis
EBM	Evidence-Based Medicine
EVA	EndoVenous Ablation
EVLA	EndoVenous Laser Ablation
EVTA	EndoVenous Thermal Ablation
EQ-5D	EuroQol – 5D
GSV	Great Saphenous Vein
HL/S	High Ligation and Stripping
HRQoL	Health-Related Quality of Life
IQR	InterQuartile Range
MCS	Mental Component Score
MECS	Medical Elastic Compression Stockings
NHS	National Health Service
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAF	Principle Axis Factoring
PASV	Posterior Accessory Saphenous Vein
PCS	Physical Component Score
PDC	Postural Diameter Change
RCT	Randomized Controlled Trial
RFA	RadioFrequency Ablation
RMST	Restricted Mean Survival Time

SAP	Single Ambulatory Phlebectomies
SD	Standard Deviation
SDH	Spinal Disc Herniation
SF-36	Short Form with 36 questions
SFJ	SaphenoFemoral Junction
SPJ	SaphenoPopliteal Junction
SSV	Small Saphenous Vein
ST	Saphenous Trunk
SVT	Superficial Vein Thrombosis
TAP	Thermal ablation with concomitant Ambulatory Phlebectomies
UGFS	Ultrasound-Guided Foam Sclerotherapy
VAS	Visual Analogue Score
VCSS	Venous Clinical Severity Score
VEINES	Venous Insufficiency Epidemiological and Economic Studies

LIST OF CO-AUTHORS

Anke A. Biemans
Department of Dermatology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands.

Renate R. van den Bos
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Philippe P. Cuypers
Department of Vascular Surgery, Catharina Hospital, Eindhoven, The Netherlands.

Marianne G.R. De Maeseneer
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Loes M. Hollestein
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Martin Lawaetz
Danish Vein Centers, Åreknudeklinikken and Surgical Center Roskilde, Naestved, Denmark.

Michael A. Kockaert
Department of Dermatology, Albert SchweitzerHospital, Zwijndrecht, The Netherlands.

Patty J. Nelemans
Department of Epidemiology, Maastricht University Medical Center, Maastricht, The Netherlands.

Martino A.M. Neumann
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Tamar Nijsten
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Olivier Pichot
Department of Vascular Surgery, University Hospital of Grenoble, Grenoble, France.

Nadia H. Shadid
Department of Dermatology, Medical Center Haaglanden, Den Haag, The Netherlands.

Anja Sommer
Department of Dermatology, Dermatologiepratijk Sommer, Maastricht, The Netherlands.

LIST OF PUBLICATIONS

van der Velden SK, Maeseneer MGR, Pichot O, Nijsten T, van den Bos RR. Postural diameter change of the saphenous trunk in chronic venous disease. *Eur J Vasc Endovasc Surg*. 2016 Apr 15; [Epub ahead of print].

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CURRICULUM VITAE

Simone van der Velden werd 9 januari 1987 geboren te Eindhoven en groeide op in het Brabantse Aalst. In 2005 behaalde zij haar VWO-diploma aan het Sint-Joriscollege te Eindhoven. Haar interesse voor de dermatologie werd al vroeg gewekt tijdens het reguliere coschap van dit specialisme. Nadat zij in 2011 haar artsexamen aan de Universiteit van Maastricht behaalde is zij eerst gaan werken als arts niet in opleiding tot specialist (ANIOS) op de afdeling interne geneeskunde in het Maxima Medisch Centrum te Veldhoven. In 2012 stapte zij definitief over naar het specialisme dermatologie en was zij gedurende een jaar werkzaam als ANIOS op de afdeling dermatologie in het Amphia ziekenhuis. Onder supervisie van professor Nijsten, dr. De Maeseneer en dr. van den Bos begon zij in 2013 aan haar promotieonderzoek op de afdeling dermatologie van het Erasmus Medisch Centrum. Sinds 2015 is zij in opleiding tot dermatoloog.

PhD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: Simone van der Velden

PhD period: 2012–2016

Erasmus MC Department: Dermatology

Promotor: Prof.dr. T.E.C. Nijsten

Supervisor: Dr. M.G.R. De Maeseneer and Dr. R.R. van den Bos

PhD training	Year	Workload (Hours/ ECTS)
General academic skills		
– English Biomedical writing and communication	2014	3 ECTS
– Workshop Endnote	2015	0.2 ECTS
Research skills		
– Molmed course: the basic introduction course on SPSS	2013	1 ECTS
– NIHES course: markers and prognostic research	2013	2 hours
– BROK	2014	1 ECTS
– EADV course: observational studies	2014	1 hour
– EADV course: non-inferiority trials	2014	1 hour
– Research integrity, Erasmus MC, Rotterdam	2015	0.3 ECTS
Oral presentations		
– Multicenter Flebologie Overleg, Rotterdam. 'Translation of the VEINES-QOL/Sym questionnaire into Dutch'.	2010	0.5 ECTS
– The Benelux Society of Phlebology, Vaeshartelt. 'Assessing disease specifity of VEINES-QOL/SYM. Does it measure what we want to know'?	2011	1 ECTS
– Congres Cabourg IV, Cabourg, France. 'Assessing disease specifity of VEINES-QOL/SYM. Does it measure what we want to know'?	2011	1 ECTS
– Multicenter Flebologie overleg, Rotterdam. 'Single ambulatory phlebectomies *versus* thermal ablation with concomitant phlebectomies'.	2013	0.5 ECTS
– The Benelux Society of Phlebology, Dinant, Belgium. 'Management strategies in patients with varicose veins (C2-C6)'.	2014	1 ECTS
– Conference of bandagers, Eindhoven. 'New topics in phlebology'.	2015	1 ECTS
– Congres Cabourg VI, Cabourg, France. 'Predictors for recanalization of the great saphenous vein after endovenous thermal ablation'.	2015	1 ECTS
– The Benelux Society of Phlebology, Kijkduin. 'Five-year results of a randomized clinical trial of CS, EVLA and UGFS in patients with great saphenous varicose veins'.	2015	1 ECTS
– EADV. 'Five-year results of a randomized clinical trial of CS, EVLA and UGFS in patients with great saphenous varicose veins'.	2015	1 ECTS
– Multicenter Flebologie overleg, Rotterdam. 'Positional variability of the saphenous trunk'.	2015	0.5 ECTS

– Wetenschappelijke vergadering NVDV. 'Five-year results of a randomized clinical trial of CS, EVLA and UGFS in patients with great saphenous varicose veins'.	2015	1 ECTS
– Journéé de la Société Française de Phlébologie, Paris, France. 'Management strategies in patients with saphenous incompetence'.	2015	1 ECTS
– UIP Chapter Meeting, Rome, Italy. 'Do age, BMI and comorbidities influence treatment strategies of patients with CVD?'.	2016	1 ECTS
– The Benelux Society of Phlebology, Gent, Belgium. 'Focus op behandeling van zijtakken'.	2016	1 ECTS
Conferences		
– 52th Annual meeting of the German society of Phlebology, Aachen, Germany	2010	1 ECTS
– 12e wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor experimentele Dermatologie, Lunteren	2011	1 ECTS
– The Benelux Society of Phlebology, Vaeshartelt	2011	1 ECTS
– Congres Cabourg IV, Caboug, France	2011	1 ECTS
– The Benelux Society of Phlebology, Oisterwijk	2013	1 ECTS
– Charing cross international symposium, London, UK	2014	1 ECTS
– Congres Cabourg IV, Cabourg, France	2014	1 ECTS
– The Benelux Society of Phlebology, Dinant, Belgium	2014	1 ECTS
– European Academy of Dermatology and Venereology, Amsterdam	2014	1 ECTS
– European Academy of Dermatology and Venereology, Copenhagen, Denmark	2015	1 ECTS
– American College of Phlebology, Orlando, USA	2015	1 ECTS
– Journéé de la Société Française de Phlébologie, Paris, France	2015	1 ECTS
– UIP Chapter Meeting, Rome, Italy	2016	1 ECTS
– The Benelux Society of Phlebology, Gent, Belgium	2016	1 ECTS
Committees		
– Organizing Multicenter Phlebology Meeting, Erasmus MC, Rotterdam	2013	1 ECTS
– Organizing 3th PhD weekend, Wassenaar	2015	1 ECTS
Teaching		
– ICK onderwijs. Introductie in de flebologie, Erasmus MC, Rotterdam	2013-2015	20 hours
Scientific awards		
– André Davy award, oral presentation at Cabourg IV flebology conference, Cabourg, France	2011	
– Benelux grant, oral presentation at Benelux society of Phlebology, Vaeshartelt	2011	
– Research grant. Benelux society of Phlebology, Dinant, Belgium. Project: SAPTAP study.	2014	
– ZonMw grant, the Netherlands Organisation for Health Research and Development Project: SAPTAP study	2014	
– Benelux grant, oral presentation at Benelux Society of Phlebology, Kijkduin	2015	
– Scholarship, American college of Phlebology.	2015	
Other		
– PhD day, Erasmus MC, Rotterdam	2013	6 hours
– Methodenuur Dermatologie, Erasmus MC, Rotterdam	2013-2015	50 hours

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