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THE MODERN TREATMENT OF VARICOSE VEINS

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*We are trying to prove ourselves wrong as quickly as possible,
because only in that way can we find progress.*

Richard P. Feynman

To Sami and Joona, with love

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I. Venermo M, Saarinen J, Eskelinen E, Vähäaho S, Saarinen E, Railo M, Uurto I, Salenius J, Albäck A; Finnish Venous Study Collaborators. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. *Br J Surg*. 2016 Oct;103(11):1438-44.
- II. Vähäaho S, Halmesmäki K, Albäck A, Saarinen E, Venermo M. Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins. *Br J Surg*. 2018 May;105(6):686-691.
- III. Vähäaho S, Mahmoud O, Halmesmäki K, Albäck A, Noronen K, Vikatmaa P, Aho P, Venermo M. Randomized clinical trial of mechanochemical and endovenous thermal ablation of great saphenous varicose veins. *Br J Surg*. 2019 Apr;106(5):548-554.
- IV. Vähäaho S, Halmesmäki K, Mahmoud O, Albäck A, Noronen K, Venermo M. Mechanochemical vs. thermal ablation of great saphenous veins: three-year results of a randomized controlled trial. Submitted.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

AASV	anterior accessory saphenous vein
ABPI	ankle-brachial pressure index
AVVQ	Aberdeen varicose veins questionnaire
AB	atrophie blanche
BMI	body mass index
CA	cyanoacrylate
CAE	cyanoacrylate embolization
CEAP	(Clinical, Etiology, Anatomy, Pathophysiology) classification system
CVI	chronic venous insufficiency
DDUS	duplex Doppler ultrasound
DVT	deep venous thrombus
EHIT	endovenous heat-induced thrombosis
ESVS	European Society for Vascular Surgery
EVSA	endovenous steam ablation
EVLA	endovenous laser ablation
FV	femoral vein
GSV	great saphenous vein
HIFU	high-frequency ultrasound
HL	high ligation
HL+S	high ligation and stripping
LDS	lipodermatosclerosis
NICE	National Institute for Health and Care Excellence (UK)
NTA	non-thermal ablation
MOCA	mechanochemical ablation
OR	odds ratio
PAOD	peripheral arterial occlusive disease
PE	pulmonary embolism
PFO	patent foramen ovale
PLAR	phlebitis-like abnormal reaction
PROM	patient-reported outcome measure
PTV	preterminal valve
PV	popliteal vein
QALY	quality-adjusted life-year
RFA	radiofrequency ablation
RCT	randomized controlled trial
SFJ	saphenofemoral junction
SPJ	saphenopopliteal junction
SSV	small saphenous vein
STP	superficial thrombophlebitis
STS	sodium tetradecyl sulphate
TGF- β 1	transforming growth factor β 1
TV	terminal valve
UGFS	ultrasound-guided foam sclerotherapy

UIP	Union Internationale de Phlébologie
VAS	visual analogue scale
VFT	venous filling time
VCSS	Venous Clinical Severity Score

TIIVISTELMÄ

Suonikohjut ovat pinalaskimoiden vajaatoiminnan tavallisin ilmentymä: riippuen suonikohjujen määritelmästä, niitä on yli 30 prosentilla aikuisväestöstä. Useimmiten kohjut aiheutuvat ison tai pienen kehräslaskimon vajaatoiminnasta, ja sen vuoksi pinalaskimovajaatoiminnan hoidoista monet keskittyvät näiden laskimoiden hoitamiseen. Kaikkien hoitomuotojen tavoitteena on tukkia tai poistaa sairas pinalaskimo. Viimeisen vuosikymmenen aikana suonensisäiset, vähemmän kajoavat hoitomuodot ovat syrjäyttäneet avokirurgian pinalaskimovajaatoiminnan hoidossa, mutta niiden pitkäaikaistuloksista on ollut niukasti tietoa saatavilla.

Tämän tutkimuksen tavoitteena on verrata ultraääniohjattua vaahtohoitoa ja suonensisäistä laserablaatiota (lämpökateetrialla tukkeamista) perinteiseen avokirurgiaan, joka koostuu suonon proksimaalisesta ligeerauksesta ja koko suonon poistamisesta ns. strippaamalla, sekä tutkia mekanokemiallista ablaatiota (mekanokemiallista tukkeamista) verrattuna laserablaatioon ja suonensisäiseen radiofrekvenssiablaatioon (myöskin lämpökateetrihoito). Ensisijaisesti tutkittiin hoidetun suonon tilaa (umnessa/poistettu, avoin tai osittain auennut); myös elämänlaatu, suonikohjujen mahdollinen uusiutuminen ja uusiutumien alkuperä olivat kiinnostuksen kohteena.

Tutkimuksen ensimmäiseen osaan kutsuttiin mukaan Helsingin ja Tampereen yliopistollisten sairaaloiden laskimopoliklinikalla käyneitä potilaita, joilla oli ison kehräslaskimon vajaatoiminta. Heidät satunnaistettiin saamaan hoidoksi joko vaahtohoito, laserablaatio tai avokirurgia. Toisessa osassa myöskin ison kehräslaskimon vajaatoiminnasta kärsiviä potilaita pyydettiin osallistumaan tutkimukseen ja heidän hoitomuotonsa valittiin satunnaisesti mekanokemiallisen ablaation, laserablaation ja radiofrekvenssiablaation välillä. Alkututkimukseen kuului ultraäänitutkimus, jossa mm. ison kehräslaskimon läpimitta mitattiin ultraäänellä. Lisäksi kliininen tilanne kirjattiin ylös ja potilaat täyttivät pinalaskimovajaatoiminnalle spesifisen elämänlaatukyselyn. Hoidon aiheuttama kipu rekisteröitiin VAS-asteikolla (Visual Analogue Scale), ja potilaiden saama kipulääkitys kirjattiin ylös. Potilaat kävivät seurantavastaanotolla kuukauden ja vuoden kohdalla; tutkimuksen ensimmäisen vaiheen potilailla oli lisäksi seurantakäynti viiden vuoden kohdalla ja toisen vaiheen potilailla kolmen vuoden kohdalla. Joka tutkimuskäynnillä tehtiin ultraäänitutkimus, kliininen tilanne kartoitettiin ja potilaat täyttivät elämänlaatukyselyn. Mahdolliset kohjujen uusiutumiset ja tehdyt lisätoimenpiteet kirjattiin ylös. Jos potilaalla todettiin vaivoja aiheuttava pinalaskimovajaatoiminnan uusiutuma, hänelle suunniteltiin tarvittaessa uusi hoito.

Yhteensä 233 potilasta oli halukkaita osallistumaan tutkimuksen ensimmäiseen vaiheeseen. Osalla kuitenkin jokin poissulkukriteeristä täyttyi, joten lopulta tutkimuksen puitteissa 214 potilasta (196 Helsingissä, 18 Tampereella) sai heille

satunnaistetun hoidon. 65 potilasta hoidettiin avokirurgialla, 68 laserablaatiolla ja 76 vaahtohoidolla. Vuoden kuluttua seurantakäynnille osallistui 96,3% potilaista. Vaahtohoito oli vähiten kivulias hoitomuoto ja sillä hoidetut potilaat tarvitsivat vähemmän sairaalomaata kuin muut, mutta vuoden kuluttua vain 51,4% vaahtolla hoidetuista suonista oli pysynyt tukossa, kun laserablaatiolla hoidetuista tukossa oli 96,7%; ero on tilastollisesti merkitsevä ($P < 0.001$). Elämänlaadun suhteen hoitoryhmissä ei ollut eroa toisiinsa nähden. Viiden vuoden kohdalla 166 Helsingissä hoidettua potilasta 196:sta (84,7%) saapui seurantakäynnille. Hoidetuista suonista ummessa (tai kokonaan poissa) oli 96,0% avokirurgian ryhmässä, 89,4% laserablaatioryhmässä ja 50,8% vaahtohoitoryhmässä ($P < 0.001$). Osa vaahtohoitoryhmän potilaista oli jo kuitenkin saanut lisähoitoa: niillä potilailla, jotka eivät olleet saaneet mitään lisähoitoa, oli ummessa 41,0% hoidetuista suonista. Vaahtohoidolla hoidettujen potilaiden todennäköisyys tarvita lisähoitoa oli 8,7-kertainen verrattuna laserablaatioryhmään. Elämänlaadussa ei ollut tilastollisesti merkitseviä eroja ryhmien välillä.

Tutkimuksen toisessa vaiheessa 132 siihen soveltuvaa potilasta ilmaisi suostumuksensa tutkimukseen; osa kuitenkin perui halukkuutensa ja lopulta hoidettiin 125 potilasta, joista 59 oli satunnaistettu mekanokemiallisen ablaation ryhmään (yhdele tässä ryhmässä tehtiin laserablaatio, mutta hänet analysoitiin mekanokemiallisen ryhmän mukana intention to treat-periaatteen mukaisesti), 34 laserablaatioryhmään ja 32 radiofrekvenssiablaation ryhmään. Kaikille potilaille tehtiin ison kehräslaskimon ablaatio ja sen jälkeen pintakohjujen poisto kirurgisesti pienten pistohaavojen kautta. Toimenpiteen aikana koetussa kivussa ei ollut eroa hoitoryhmien välillä, mutta mekanokemiallisen ablaation ryhmässä potilaat saivat vähemmän kipu- ja rauhoittavaa lääkitystä toimenpiteen aikana. Sairaslomat olivat tilastollisesti yhtä pitkiä kaikissa ryhmissä.

Vuoden kohdalla 93,6% potilaista osallistui seurantakäynnille. Mekanokemiallisen ablaation ryhmässä oli ummessa 81,8% hoidetuista suonista, ja suurin osa suonien aukeamisista oli osittaisia; laserablaatio- ja radiofrekvenssiablaatioryhmissä ummessa oli 100% hoidetuista suonista. Mekanokemiallisen ablaation ryhmän potilaista yhdelläkään ei ollut tunnon alenemaa tai -muutosta hermovaurioon viitaten, sen sijaan neljällä laserhoidetulla ja kolmella radiofrekvenssihoidetulla potilaalla oli tunnon alenemaa pienellä ihoalueella. Kolmen vuoden seurantakäynnille saapui 106 potilasta (84,4%). Hoidettu suoni oli edelleen ummessa 100%:lla radiofrekvenssi- ja laserablaatiopotilaista ja 82,0%:lla mekanokemiallisesti hoidetuista potilaista ($P = 0.005$). Ilman lisätoimenpiteitä ummessa oli pysynyt 80,0% mekanokemiallisesti hoidetuista suonista. Niillä potilailla, joilla hoidettu suoni oli näkynyt osittain auenneena vuoden kohdalla, oli suoni ajan mittaan auennut laajemmalla alueella. Koetussa elämänlaadussa ei ollut tilastollisesti merkitseviä eroja ryhmien välillä.

Johtopäätöksenä voidaan todeta, että laserablaatio on vähintään yhtä hyvä hoitomuoto kuin avokirurgia viiden vuoden seurannassa; mahdolliset komplikaatiot

ja kustannukset huomioiden laserablaatio on selvästi parempi. Sen sijaan huomattavan suuri osa vaahtohoidetuista laskimoista aukeaa uudelleen ajan kuluessa. Mekanokemiallisella ablaatiolla hoidetuista suonista merkitsevästi suurempi osa aukeaa seurannassa kuin laser- tai radiofrekvenssiablaatiolla hoidetuista suonista; toisaalta mekanokemiallisen ablaation ryhmässä ei todettu yhtäkään hermovaurioon viittaavaa ihon tunnon alenemaa. Elämänlaadussa ei voitu todeta eroja eri hoitomuotojen välillä.

ABSTRACT

Background: Varicose veins are caused by superficial venous insufficiency and are very common, with a prevalence of over 30% in adults. Varicose veins are in most instances caused by great saphenous vein (GSV) or small saphenous vein (SSV) insufficiency, and consequently many treatment methods base on obliterating the defective vein. During the last decade, the treatment of superficial venous insufficiency has undergone a fundamental change from open surgery to less invasive, endovenous methods. Not much data on the long-term results of these methods has been published, though endovenous methods have replaced open surgery in many centres and thermal ablation has by this time become the new gold standard.

Aims: The aim of this thesis is to compare the results of ultrasound-guided foam sclerotherapy (UGFS) and endovenous laser ablation (EVLA) to conventional open surgery consisting of high ligation and stripping, and to study mechanochemical ablation (MOCA) in contrast to EVLA and radiofrequency ablation (RFA), both of which are currently well-established treatment methods. The technical success in view of the GSV occlusion rate, the gain in quality of life as well as recurrence rate and pattern are of interest.

Methods: Outpatient clinic patients presenting with GSV insufficiency in one leg were invited to participate in the studies. In the first part of the studies, the patients were randomized to receive either UGFS, EVLA or open surgery. In the second part, the randomization was to either MOCA, EVLA or RFA treatment. Prior to treatment, the patients filled Aberdeen Varicose Vein Questionnaire (AVVQ), a tool designed to measure the disease-specific quality of life. The diameter of the GSV was recorded using duplex Doppler ultrasound (DDUS). The experienced pain was described in the visual analogue scale (VAS) during the treatment, at the time of the discharge and at one week postoperatively. The amount of received pain medication was recorded. In the first part of the study, the patients were followed up at one year and five years after the treatment; in the second part of the study, the follow-ups took place at one year and three years. The follow-up included the AVVQ, DDUS examination and clinical status; recurrence, any additional treatment or the need for such in addition to possible complications were recorded.

Results: 233 patients were randomized in the first part of the study; some, however, met an exclusion criteria not recognized at the time of recruitment or were not willing to continue in the study. In total, 214 patients finally underwent treatment (18 in Tampere University Hospital and 196 in Helsinki University Hospital): 65 received open surgery, 68 EVLA and 76 UGFS. At one-year follow-up, the participation rate was 96.3%. UGFS had some initial benefits compared to EVLA and open surgery, being virtually pain-free and requiring only a short sick leave, if at all. However, the GSV remained occluded or absent only in 51.4% of the UGFS-

treated patients compared to 96,7% of those treated with EVLA or open surgery ($P < 0.001$). The disease-specific quality of life did not differ between the treatment groups. At five years, 166 of the 196 (84.7%) patients treated at Helsinki University Hospital attended the follow-up. The occlusion rate of the GSV was 96.0% in the open surgery group, 89.4% in the EVLA group, and 50.8% in the UGFS group ($P < 0.001$). Yet, some patients had already received repeat treatment, and the non-assisted occlusion rate was only 41.0% in the UGFS group. The odds of needing additional treatment was 8.7 times greater for UGFS than for EVLA. The disease-specific quality of life did not significantly differ between the groups, but a tendency towards a higher AVVQ score in the UGFS group reflecting lower quality of life was observed.

In the second part of the studies, 132 patients with GSV insufficiency in one leg agreed to participate in a randomized trial comparing MOCA with EVLA and RFA. Again, some patients declined to participate after randomization. Ultimately, 59 patients in the MOCA group (with one patient crossing over to EVLA, but analysed in the MOCA group), 34 in the EVLA group and 33 in the RFA group underwent treatment: the ablation of the GSV with the randomized method and concomitant phlebectomies. The perceived pain did not differ between the groups at any time point, but the patients in the MOCA group received less sedatives during the procedure. The duration of the sick leave was equal between the groups. At one-year follow-up with an attendance rate of 93.6%, the occlusion rate of the GSV was 81.8% in the MOCA group and 100% in both the EVLA and RFA groups ($P = 0.002$). Most of the recanalizations in the MOCA group were partial. In the MOCA group, no sensory disturbances (signs of nerve injury) were observed, while four patients in the EVLA group and three in the RFA group reported such disturbances. At three years, 106 patients (84.8%) attended the follow-up. The occlusion rates at this point were 82.0% for MOCA and 100% for the EVLA and RFA groups ($P = 0.005$); the unassisted occlusion rate was slightly lower, 80.0% in the MOCA group. In the MOCA group, the partial or complete recanalizations of the proximal GSV seen at one year had progressed, leading to further recanalization of the GSV. The disease-specific quality of life was not statistically different between the treatment groups.

Conclusions: EVLA is at least as good as open surgery in a follow-up of up to five years; when possible complications and costs are considered, EVLA is superior. In contrast, despite having immediate advantages over more invasive treatment methods, UGFS leads to a low occlusion rate and far more additional treatments compared to either EVLA or open surgery. MOCA appears inferior to thermal ablation with EVLA or RFA regarding the occlusion rate, though it seems to cause no nerve injuries. The disease-specific quality of life did not statistically differ between the treatment groups.

INTRODUCTION

Varicose veins are an extremely common ailment, affecting at least 30% of adult population (Evans et al. 1999, Brand et al. 1988, Carpentier et al. 2004, Franks et al. 1992, Rabe et al. 2012). Varicose veins are a visible manifestation of superficial venous insufficiency. Besides being cosmetically unappealing, superficial venous insufficiency can cause a plethora of symptoms including swelling in the leg, pain, itching, thrombophlebitis, skin discoloration and even ulcers; the prevalence of venous ulcers has been recorded as being approximately 1% (Ruckley et al. 2002). Chronic venous insufficiency (CVI) can consist of either superficial or deep venous insufficiency, or both. The term CVI is generally used when the disease is more advanced, causing skin changes. Varicose veins were responsible for a £40 million expenditure in Great Britain in 2005–2006, and venous ulcers have been estimated to account for 1–2% of the health care expenses in Western countries (Onida and Davies 2016). The most common superficial vein to be insufficient is the great saphenous vein (GSV) (Maurins et al. 2008). This thesis therefore concentrates on the treatment of GSV insufficiency.

The treatment of superficial venous insufficiency is currently undergoing a fundamental change. Compression hosiery has been in the physicians' toolbox for centuries and surgery on varicose veins has been practiced since ancient before the Common Era, with greater or smaller success. The gold standard of treatment was for long been open surgery involving ligating and removing the culprit vein. The open surgical procedure is usually done under general anaesthesia and too often performed by the youngest surgical trainee. The open procedure predisposes the patient to many complications as well as having a lengthy recovery period. Also, surgery does not prevent recurrence, which occurs down the line in most of the patients (Campbell et al. 2003).

Since the advent of duplex Doppler ultrasound, the diagnostics have improved, and new, minimally invasive treatments have arrived, relying on ultrasound guidance during the operation. Ultrasound-guided foam sclerotherapy is an example of least possible invasiveness: the whole procedure can be performed through a few small cannulas or even butterfly needles; it is painless and usually no sick leave is required. In practice, however, the results have often been less than optimal, but the advocates of foam sclerotherapy emphasize the ease of repeating the treatment if necessary.

At present, endovascular ablation methods have, with good reason, become the most common treatments for venous insufficiency and are now recommended as the first line treatment for saphenous vein insufficiency by the Guidelines of European Society for Vascular Surgery as well as by the Finnish Current Care Guidelines (Wittens et al. 2015, Current Care Guidelines 2016). Endovascular ablation is less invasive and less painful for the patient than open surgery, the

recovery after the procedure is faster and it can be performed in an outpatient setting. The prevailing ablation methods are based on thermal energy, and to be applied safely and painlessly, they need the application of a liquid barrier (tumesence solution) between the treated vein and the adjacent tissues. If the procedure is successful, the treated vein remains occluded or subsequently shrinks, leaving only a fibrotic scar. In endovascular ablation, the proximal orifice of the vein remains open unlike in surgery, and this has aroused the question of durability of the occlusion in the long term.

To overcome the cumbersome administration of tumescence and the risk of thermal injury, non-thermal ablation methods are being developed. They seem to be fast to apply and comfortable to the patient. However, the data on the long-term efficacy and safety of the methods is currently scarce.

REVIEW OF THE LITERATURE

1 SUPERFICIAL VENOUS INSUFFICIENCY: AETIOLOGY AND DIAGNOSTICS

1.1 Anatomy and physiology

Deep veins of the leg return blood back to central circulation. In the leg, there are paired deep veins in each fascial compartment of the leg: the peroneal (fibular) veins, anterior tibial veins, and posterior tibial veins. These coalesce at around the knee to form the popliteal vein (PV), which continues upwards in the thigh as the femoral vein (FV). In the thigh, the femoral vein and the deep femoral vein join to form the common femoral vein (CFV). Since blood ascends against gravity, the propulsion of blood back to the heart is all but dependent on the action of the foot, calf, and thigh muscle pumps, with the calf pump being the most important. Also assisting in venous flow are breathing, since it creates negative intrathoracic pressure, and compression of the veins by the accompanying arteries.

Superficial veins drain the cutis and subcutis and are located above the fascia. Two main axial superficial vein trunks exist: the great saphenous vein (GSV) and the small saphenous vein (SSV). These drain into the deep venous system: the SSV usually into the popliteal vein in the popliteal fossa (saphenopopliteal junction [SPJ]), and the GSV into the common femoral vein in the groin, forming the saphenofemoral junction (SFJ). There are also other, accessory superficial veins and intersaphenous veins connecting the GSV and SSV. The superficial and deep venous system are connected via hundreds of small perforating veins that pierce the fascial layers. Both the GSV and the SSV are enclosed in their own compartment that is bound anteriorly by a thin layer of connective tissue called the saphenous fascia, and deeply by the muscular fascia. The anterior accessory saphenous vein (AASV) ascends parallel and anteriorly and the posterior accessory saphenous vein posteriorly to the GSV (Caggiati et al. 2002). The GSV is the commonest superficial vein to be insufficient, i.e. to cause venous symptoms and findings, such as varicosities; the SSV comes second (Maurins et al. 2008).

In most individuals, the thigh GSV lies in the saphenous compartment and no parallel large tributaries are seen. Anatomic variation is, however, common: there can be a parallel subcutaneous tributary that joins the GSV at a variable level; the proximal GSV can lie in the saphenous compartment but be absent distally, with a subcutaneous tributary in continuum with the GSV; the AASV can join the GSV well below the SFJ; or rarely – in about 1% of the population – the GSV is duplicated.

Around and below the knee, there are many tributaries and perforators, and the anatomy is even more variable (Chen and Prasad 2009, Ricci and Caggiati 1999).

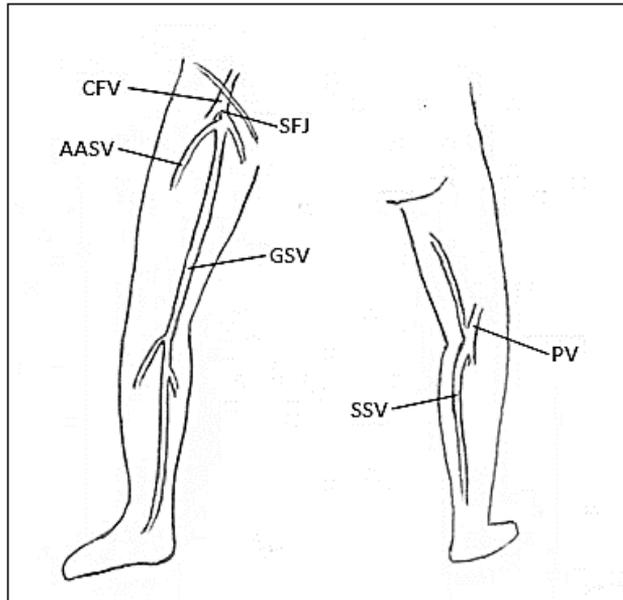


Figure 1. Superficial venous anatomy of the leg

In both superficial and deep veins, there are valves that inhibit reflux (retrograde flow of blood). The valves are formed from folds of the endothelium (Meissner 2005). The valves are bicuspid and unidirectional, and they close when the flow velocity decreases and the valve sinus dilates as the calf muscle relaxes (Lurie et al. 2002). Perforating veins of the calf, however, might not have valves at all, and they present bidirectional flow, with the direction of the flow depending on the contraction and relaxation of the calf muscles, forming a kind of pressure-equilibrating system (Recek 2016). The most important valves of the GSV are the terminal valve (TV), located at the saphenous opening to the CFV, and the preterminal valve (PTV), located a few centimetres below. The number of valves varies between individuals, and the frequency of valves increases distally in healthy veins.

1.2 Pathophysiology

The underlying cause of venous insufficiency and varicose veins is not completely understood, although there are many theories and known risk factors.

The descending, or saphenocentric, theory of venous insufficiency was first proposed by Trendelenburg in 1890 (Royle and Somjen 2007). In this theory, increased intra-abdominal pressure, precipitated by obesity, multiparity and long-term standing, is transmitted caudally to the veins, rendering valves incompetent. This leads to a vicious cycle of further pressure and dilatation aggravating the valvular incompetence. According to this theory, TV incompetence is the root cause of insufficiency in the GSV. However, it has been shown that GSV reflux is not always accompanied by SFJ reflux (Labropoulos et al. 2000) and that the TV can be competent in the presence of SFJ reflux in up to 24.8% of patients with GSV reflux (Zollmann et al. 2017). This descending theory is, nonetheless, the basis of most treatment methods for GSV reflux. This theory is supported by the Bochum study, in which 740 children aged 10 to 12 years were examined for venous reflux and observed longitudinally for up to 29-31 years of age. Initially, a preclinical saphenous vein reflux was observed in 2.5% of the children. Most of them developed clinical varicose veins in the course of the study. The incidence of varicose veins was found to increase with age, as did the length of the GSV reflux. The authors concluded that in most cases, varicose veins are preceded with truncal reflux (Schultz-Ehrenburg et al. 2009).

According to the ascending theory, when standing, the pressure of the venous pillar in the leg, combined with the intrinsic weakness of the vein walls, leads to the distension of the distal veins, creating a venous reservoir. Distal varicosities fill and create an ascending column of hydrostatic pressure. Thus, reflux is first created distally, and with time, the reflux spreads proximally (Onida and Davies 2015, Jacobs et al. 2017).

Neither of these haemodynamic theories fully explain the pathogenesis. New studies focus on the vein wall, hypothesizing that local factors cause the weakening of the wall structure, leading to the dilatation of the vein, which in turn promotes valve incompetence when the valve cusps no longer meet. Plenty of studies concentrate on the cellular changes in varicose veins that are complex and affect one another.

Macroscopically, in venous insufficiency, the affected veins have areas of normal vein between varicosities. In some places, the veins are hypertrophied, and in others, varicosities form. The varicosities themselves have an increased luminal diameter and intimal hypertrophy. In the vein walls the connective tissue is abnormally accumulated among the smooth muscle cells, inhibiting their normal action (Jacobs et al. 2017, Segiet et al. 2015). The amount and arrangement of elastin and collagen fibres are abnormal. Smooth muscle cells are disorganized, and their contractile function is impaired (C. S. Lim and Davies 2009).

At the point when varicose veins appear, both the vein wall changes and the disruption of the valves are already present, and the true sequence of events cannot be determined – this is a “hen or egg” problem. However, it is thought that

hydrostatic pressure of the venous system that is exacerbated by long-term standing and pregnancy might cause injury to the vein wall, leading to changes in its structure and facilitating valvular dysfunction (C. S. Lim and Davies 2009). In conclusion, the aetiology of varicose veins is multifactorial, with various elements contributing to a cycle of events, each aggravating the condition.

1.3 Epidemiology

1.3.1 The prevalence of varicose veins

Prevalence estimates of varicose veins vary in different reports. This is due to differences in reporting and classification. Some studies use questionnaires answered by the study participants, while other studies report the findings made by a study team employing strict criteria for varicose veins; yet another type of study asks the patients whether a doctor has made a diagnosis of varicose veins (Beebe-Dimmer et al. 2005). The concept of varicose veins might not be clear to people, and especially men are not prone to complaining about minor varicosities, and at least these questionnaire-type studies are thus susceptible to error. In the Finnish Tampere Vein Study, the specificity of the self-assessed diagnosis was lower in men and in those individuals who reported a positive family history for varicose veins (Laurikka et al. 1995).

One of the most cited studies is the Edinburgh Vein Study, in which 1,566 individuals were screened for varicose veins. Telangiectasia, also known as spider webs – small, under 1 mm, dilated blood vessels near the surface of the skin – were extremely common, affecting over 80% of the participants (Evans et al. 1999). Reticular veins were also seen very often, in over 80% of the participants. Neither of these entities is usually considered to constitute proper varicose veins, but this highlights the problem of classifying and reporting. In the Edinburgh Vein Study, truncal varicosities and their branches “of the first and second order” were present in 39.7% of men and 32.2% of women; these can be considered “varicose veins proper”.

Another famous study, the Framingham Study, followed the men and women living in Framingham over a 16-year period. An examination for varicose veins took place every second year, and at the end, 23% of the men and 31% of the women who were free from varicosities at the beginning of the study had developed varicose veins (Brand et al. 1988). In a study population in France, some 50.5% of women and 30.1% of men had varicose veins in a clinical examination; telangiectasia and reticular veins were not included in these numbers (Carpentier et al. 2004). In the Basle Study II, 4,422 employees of the chemical industry were screened for varicose veins, and the prevalence was found to be 57% in men and 68% in women, but this included all types and grades of varicosities (da Silva et al. 1974). In another study in Switzerland, the

presence of varicose veins was examined in 610 women working in department stores, and a prevalence of 29.0% was found. This number did not include telangiectasia and reticular veins (Guberan et al. 1973). In West London, in a sample of people aged 35–70 years, 31% had some form of venous disease, with varicose veins being most common (Franks et al. 1992). In the Tampere Vein Study conducted in Finland, the prevalence of varicose veins was 25% in women and 7% in men (Sisto et al. 1995). More recently, results from the Vein Consult Program, an international prevalence study, were published. This study enrolled 91545 patients seen by general practitioners for nonacute reasons. The overall prevalence of CVI was reported to be 83.6%; however, patients that were symptomatic yet had no visible signs of CVI constituted up to 19.7% of the study population. Varicose veins, swelling and skin changes were present in 56.9% of the study subjects (Rabe et al. 2012).

Callam et al. reviewed all studies investigating the prevalence of varicose veins conducted before 1994; they estimated that, in an unselected Western population over the age of 15, the prevalence of visible varicose veins would be 10–15% for men and 20–25% for women (Callam 1994).

The majority of studies on varicose vein prevalence are conducted in Western countries, and the general consensus seems to be that varicosities are less common in underdeveloped regions. In a study conducted in Tanzania, the prevalence of varicose veins was 5.5% (Richardson and Dixon 1977). Mekky et al. examined women working in cotton mills in both England and Egypt, finding that the prevalence of varicose veins was 32% in European women and 6% in Egypt. This difference was, however, thought to be environmental rather than ethnic (Mekky et al. 1969). In Brazil, the presence of moderate or severe varicose veins among 1755 adults was found to be 21.2% and higher in Caucasian than non-Caucasian individuals; the overall prevalence did not differ from Western countries (Maffei et al. 1986). The San Diego Population Study examined 2211 men and women for venous disease, utilising both ultrasound (superficial and deep functional disease) and clinical examinations (visible varicose veins), and found that non-Hispanic whites had a higher prevalence of both visible and functional disease than minorities in general. An exception was Hispanics, who had a slightly higher prevalence of varicose veins and superficial functional disease. Asians, in contrast, had the lowest prevalence (Criqui et al. 2003). This is in line with the study by Hirai et al., which reported that varicose veins were less common in Japan than in Western countries, with a total prevalence of 45% including telangiectasia and reticular veins (Hirai et al. 1990). In Lowland New Guinea, the prevalence of varicose veins has been found to be very low – 0.1% or one of 729 women and 5.1% in men (Stanhope 1975). Interestingly, in the South Pacific, the prevalence of varicose veins differed greatly from one area to another. In New Zealand, the age-standardized prevalence was 33.4% for women and 43.7% for men; in Ratoronga,

the prevalence was 15.6% and 14.9%, and in Tokelau Island, 2.9% and 0.8%, respectively. Body mass, parity, age, etc., were excluded from being responsible for this difference in a multivariate analysis (Beaglehole et al. 1975). In conclusion, the prevalence varies greatly geographically, but the reasons for the variation are not evident.

1.3.2 Risk factors

1.3.2.1 Age

It is accepted that varicose veins become more common with age (Beebe-Dimmer et al. 2005, Callam 1994, Robertson et al. 2008). In the Edinburgh Vein Study, the prevalence of trunk varicosities was 11.5% among participants aged 18–24 years, compared to the 55.7% among the age group of 55–64-years (Evans et al. 1999). The Tampere varicose vein study surveyed 40-, 50-, and 60-year old residents of Tampere, Finland, for varicose veins with questionnaires; in this study, the crude OR for varicose veins was 1.9 for 50-year olds and 2.5 for 60-year olds, in comparison to 40-year olds (J. O. Laurikka et al. 2002). Mekky found that, among European women working in the cotton mills in England, the prevalence of varicosities rose with age (Mekky et al. 1969). In the San Diego Population Study, the prevalence of varicose veins was 16.9% among under 50-year-olds and 29.9% in the group of participants aged 70 years or older (Criqui et al. 2003). In the Framingham Study, the incidence of varicose veins was examined through the 16-year period, and age had no clear effect on the incidence in either sex (Brand et al. 1988). In summary, varicose veins cumulate with age.

1.3.2.2 Gender

In most studies, the prevalence of varicose veins is evidently greater in women than in men. Questionnaire-based studies may exaggerate the proportion of women, however, and some study samples include an uneven number of women and men. In his review of previous studies, Callam concluded that the female-to -male-ratio was between 1.5:1 and 3.5:1 (Callam 1994). In the Tampere varicose vein study, the odds ratio (OR) for varicose veins was 3.2:1 for females compared with males (Laurikka et al. 2002). In a study conducted on the working population of Rijeka, varicose veins were diagnosed in 34.6% of women and 18.9% of men (OR 1.84) (Kontosic et al. 2000). Both spider veins (55.9% vs 4.6%) and varicose veins (27.7% vs 15.0%) were more common in women than in men in the San Diego Population Study (Criqui et al. 2003). In Tecumseh, located in Michigan, USA, some 25.9% of women and 12.9% of men were found to have varicose veins (Coon et al. 1973). In contrast, in the Edinburgh Vein Study, trunk varicosities were present in 33.3% of men and 26.2% of men; women had a higher prevalence for hyphenweb (teleangiectatic) and reticular varices than men (Evans et al. 1999), and in the

Lowland New Guinea, men had a higher prevalence of 5.1% compared to the 0.1% in women (Stanhope 1975).

Some studies propose that although varicosities are more common in women, chronic venous disease with trophic changes or ulcers is more common in elderly males. In the Edinburgh Vein Study, in the age group of 55–64 years, the prevalence of either corona phlebatica, pigmentation or hypopigmentation, and that of open or healed ulcers was much higher in men (25.2%) than in women (12.3%), although most of the changes were mild (Evans et al. 1999). In 93 CVI patients treated for lipodermatosclerosis or venous ulcers, the OR was 2.9 for male sex (Scott et al. 1995). In contrast, in Tecumseh, some 3.0% of men and 3.7% of women had static skin changes, and a respective 0.1% and 0.3% had an active or healed ulcer (Coon et al. 1973).

1.3.2.3 Family history

Anecdotally, varicose veins are known to pass “from mother to daughter”. Studies seem to support this statement. In Japan, 42% of patients with varicose veins reported a positive family history, while only 14% of those without varicose veins reported the same (Hirai et al. 1990). In the Tampere Vein Study, a positive family history was a strong determinant of varicose veins, with an odds ratio of 4.9 (Laurikka et al. 2002); in France, the odds ratio was 3.47 (Carpentier et al. 2004). In Scott’s study in Boston, up to 85.8% of patients with varicose veins reported a positive family history, as opposed to 22.5% in the control group (Scott et al. 1995). In the Edinburgh Vein Study, the age-adjusted OR for varicose veins was 1.52 for those with a positive family history (Lee et al. 2003).

In most studies concerning risk factors, however, the family history is based on interviewing the participants or on a questionnaire. People with varicose veins are undoubtedly more aware of them in their family or might have a tendency of overreporting them. In the Tampere Vein Study, a 5-year follow-up query to the participants was made, and surprisingly, the answers differed from those given in the beginning of the study: fewer reported a positive family history at the end of the 5-year period. The authors concluded that self-reporting a family history of varicose veins is biased (Ahti et al. 2010). There are only few reports that base the family history on an actual clinical examination. In a small pilot study, 88 individuals and 90% of their first-degree relatives were examined. It was found that, when the participant had varicose veins, the family history provided and clinical examination agreed in only 52% of cases (Weddell 1969). In summary, the heritability of varicose veins is not incontrovertibly demonstrated.

1.3.2.4 Pregnancy

Pregnancy predisposes to varicose veins via several mechanisms. The haemodynamic changes are numerous (Taylor et al. 2018). In early pregnancy, the plasma volume is expanded, leading to an increase in blood volume. The growing

foetus and womb increase abdominal pressure, which hinders venous return from the lower limbs. It has been shown that both venous volume and the diameter of lower extremity veins is greater in pregnant women (Goulart et al. 2013). Hormonal mechanisms are also important, since many hormones are excreted especially during pregnancy. Relaxin, a hormone known to relax the pelvic ligaments in order to facilitate birth, also has vasodilating effects (Skott and Carter 2002). The levels of sex hormones oestrogen and progesterone are elevated in pregnant women. According to one study, oestrogen receptors are more often expressed in varicose veins, and the amount is correlated with the severity of chronic venous insufficiency (Serra et al. 2016). Another study found an abundance of progesterone receptors (but not oestrogen receptors) in varicose veins (Perrot-Appanat et al. 1995); progesterone inhibits the contraction of smooth muscle cells (Ropacka-Lesiak et al. 2012). Sex hormones might, then, be at least partially responsible for the greater prevalence of varicose veins in women.

Most studies on the epidemiology of varicose veins agree that pregnancy, and more so multiparity, are risk factors for varicose veins; according to a meta-analysis, the OR is 1.82 in comparison to women with no pregnancies (Ismail et al. 2016). In the study on cotton mill workers England and Egypt, 26.2% of nulliparous women and 35.8% of those with at least one child in the English subpopulation had varicose veins, and in Egypt, the percentages were 4.0 and 10.9, respectively (Mekky et al. 1969). In the working population in Rijeka, the OR for varicose veins was 0.93 for those with one or more pregnancies, but 1.22 for those with one or more deliveries in their history (Kontosic et al. 2000). In the Framingham Study, women who had two or more pregnancies had a higher incidence of varicose veins than those with none or one, but this difference was not statistically significant (Brand et al. 1988).

In the Edinburgh Vein Study, surprisingly, the OR of varicose veins was 0.92 for those with a pregnancy in their history (Lee et al. 2003). The study conducted in Tanzania failed to show a correlation between the number of pregnancies and varicose veins (Richardson and Dixon 1977). In the Basle Study II, it was found that, when the age factor was excluded, parity had no effect on the prevalence of varicose veins (da Silva et al. 1974). A similar observation was made by Guberan and colleagues (Guberan et al. 1973). In the South Pacific, among Maori and Pakeha women, age-standardized parity seemed to be related to varicose veins, but this was not seen among Ratorongan women (Beaglehole et al. 1975). Hirai et al. found that, in Japan, there was no relationship concerning the number of pregnancies and varicose veins (Hirai et al. 1990).

In total, the effect of pregnancy on the incidence of varicose veins, though very often anecdotally high, may only be to make the appearance of varicose veins occur earlier. Eighty percent of pregnant women present with symptoms and findings of chronic venous insufficiency (Enkin et al. 2000), but these symptoms often recede after delivery. Perhaps, as parity in the Western world is decreasing, newer studies can shed further light on this subject.

1.3.2.5 Obesity

In obesity, the intra-abdominal pressure is high, and this hinders the venous return from the lower limbs. Thus, obesity can cause symptoms that are similar to those caused by varicose veins, such as pain and swelling in the legs.

In Basle, the prevalence of varicosities seemed to be higher among obese women, but only because they were older, and after age correction, no correlation was found and the results of Guberan were analogous (da Silva et al. 1974, Guberan et al. 1973). The Mini-Finland Health Survey detected that the thinnest men and women had the lowest prevalence of varicose veins, but after the thinnest quintile was disregarded, the degree of obesity had only a slight effect (Sisto et al. 1995). In Japan, obesity was not associated with varicose veins in women (Hirai et al. 1990). Similarly, in France, a body mass index (BMI) of over 23 kg/m² for women and 25 kg/m² for men was not a risk factor for varicose veins (Carpentier et al. 2004). Mekky et al. found that, among the cotton mill workers in England, obesity had a positive association to varicose veins only in the youngest age group (Mekky et al. 1969).

Among the women in the Edinburgh Vein Study, a higher BMI was associated with a higher risk of varicose veins (age-adjusted OR 1.13), and in the Framingham Study, the incidence of varicose veins was higher for obese women (Brand et al. 1988). In the Tampere Vein Study, both weight and height had a statistically significant effect on the prevalence of varicose veins (Laurikka et al. 2002). Since the effect of BMI, if observed at all, is mostly seen in women, it has been postulated to be due to parity because the average weight of parous women is higher than that of nulliparous women (Beebe-Dimmer et al. 2005).

1.3.2.6 Long-term standing

When standing, venous pressure is increased. Thus, long-term standing, such as in a standing occupation, can be considered to be a risk factor for vein disease and varicose veins. In women working in department stores, this effect was indeed seen, as the prevalence for varicose veins was 34.5% in women standing at work compared to the 28% in other groups; this difference was, however, not statistically significant (Guberan et al. 1973). In Brazil, no effect of standing was perceived (Maffei et al. 1986). Mekky et al. observed that in European women working in cotton mills, those who worked standing up had a much higher prevalence of varicose veins than to those who either walked or sat at work (Mekky et al. 1969). In the Tampere Vein Study, the adjusted OR for varicose veins for individuals standing at work was 1.6 (Laurikka et al. 2002), and in the working population studied in Rijeka, the OR for those primarily standing at work was 1.35 (Kontosic et al. 2000). Carpentier et al. found that both prolonged sitting and standing were risk factors for varicose veins (Carpentier et al. 2004). In the Edinburgh Vein Study, a higher proportion of women with truncal varicosities reported spending more than half their working hours either standing or lifting (Lee et al. 2003). In summary,

most studies support the notion of standing occupations being a risk factor for varicose veins.

1.3.2.7 Other factors

Some studies on the aetiology of varicose veins have suggested diet, constipation or defecation posture as a potential risk factor for varicose veins, and this has been considered as one of the reasons for the larger prevalence in industrialized areas. There were considerable differences in the prevalence of varicose veins between different areas of the South Pacific: in New Zealand, where varicose veins were more prevalent, the diet was typical of industrialized countries, while in the low-prevalence Tokelau and the Cook Islands, the diet was still more indigenous, containing less sugar and higher amount of fibre (Beaglehole et al. 1975). Mekky et al. found no significant correlation between constipation and varicose veins but considered a squatting defecation position as one possible explanatory factor for the lower prevalence of varicosities among Egyptians (Mekky et al. 1969). In a study conducted in Tanzania, a squatting position during defecation was not found to be protective against the development of varicose veins (Richardson and Dixon 1977). In the Edinburgh Vein Study, no direct effect of diet or constipation was perceived (Lee et al. 2003). The most contemporary studies do not include defecation posture or fibre intake as factors, and nothing conclusive can be said about them in relation to varicose veins.

The use of girdles or corsetry has also been mentioned. Today, their use is rare, but in the cotton mill workers in England, 36% of those wearing corsetry or roll-ons (a type of girdle) were found to have varicose veins, while only 22% of those not wearing them had varicosities (Mekky et al. 1969). Guberan et al., however, found in their study that when this factor was age-adjusted, the relationship disappeared (Guberan et al. 1973).

1.4 Clinical manifestations and classification of venous disease

1.4.1 CEAP classification system

The clinical manifestations of venous disease can be classified in with the CEAP (Clinical, Etiology, Anatomic, Pathophysiology) classification system. This classification was created by an international consensus conference on chronic venous disease to provide a uniform and accurate basis for research on venous disease (Porter and Moneta 1995). The classification was further revised in 2004 to include more precise definitions (Eklof et al. 2004).

The 'C' for Clinical classification in the CEAP system is divided into six categories in an ascending order of severity in symptoms, and each category can also include symptoms and findings from a lower category. C₀ stands for no visible or palpable

signs of venous disease, denoting a healthy individual. The VEINES study compared the physician-assessed CEAP class with perceived quality of life – both venous disease-specific and general – and found that the CEAP class also reflects well the patients' perceptions of the venous disease severity (Kahn et al. 2004).

In the CEAP classification system, the 'E' stands for aetiology. This class has three subclasses: E_C for congenital venous disorders, E_P for primary venous dysfunction (of unknown cause), and E_S for secondary venous dysfunction, i.e. an acquired condition such as post-thrombotic syndrome. E_N has been added later to describe a situation with no identified venous cause.

The 'A' in the CEAP signifies anatomical classification. A_S involves superficial veins, A_D deep veins, and A_P perforating veins; the venous disease can involve any combination or all of these. A_N denotes "no venous location identified". In the original consensus statement, a list of the segmental localization of venous disease was also provided.

The 'P' represents pathology. Clinical signs or symptoms of chronic venous disease result from reflux (P_R), obstruction (P_O), or both ($P_{R,O}$). In P_N , no venous pathology can be identified.

The CEAP classification has some shortcomings. For example, it does not accurately describe the symptoms such as pain, cramps and itching; when deciding whether a patient is offered treatment for varicose veins, it is mostly symptoms and ultrasound findings that guide the decision. Also, the classification does not account for previous treatment. Therefore, while it is often used for scientific purposes, it is not often used in everyday venous practice. Presented below are the C classes that describe clinical findings.

1.4.1.1 C_1 : Telangiectasia and reticular veins

The CEAP class C_1 comprises telangiectasia and reticular veins. Telangiectasia refers to, according to the consensus statement, confluences of dilated intradermal venules less than 1mm in calibre. They are also commonly called spider veins or hyphenwebs. Reticular veins are defined as dilated bluish subdermal veins, usually 1 mm to less than 3 mm in diameter; they are usually tortuous. Synonyms for them are blue veins, subdermal varices and venulectasies.

Telangiectasia is mainly considered a cosmetic problem, and published research on their pathogenesis is scarce. Telangiectasia as the only manifestation of venous disease might be an early presentation of superficial venous insufficiency, and is not associated with either deep or venous reflux (Thibault et al. 1990). Telangiectasia is nearly constantly associated with reticular vein incompetence (Somjen et al. 1993, Weiss and Weiss 1993). Reticular vein incompetence, in turn, is thought to be caused by a failure of microvenous valves (Caggiati et al. 2006). In the Edinburgh Vein Study, the existence and severity of telangiectasia were recorded. It was more

common in women: 88% as opposed to 79% in men. Telangiectasia as the only clinical manifestation of venous disease was associated with hormone replacement therapy and a history of pregnancy, but contraceptive pill users were more frequently free from the condition. There was also a correlation between trunk varicose veins and the frequency of telangiectasia. People with class C₁ disease present with more symptoms of CVI than those with no disease (Ruckley et al. 2008).

1.4.1.2 C₂: Varicose veins

As stated in the consensus statement, varicose veins, or varicosities, are classified as subcutaneous dilated veins of 3 mm in diameter or larger, measured in an upright position. They may involve the saphenous veins, saphenous tributaries or nonsaphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may, according to the statement, be classified as varicose veins. As described in detail before, varicosities are quite common, with a prevalence of over 25% in the Western world.

The typical symptoms of varicose veins are similar to those of all venous insufficiency conditions: aching, heaviness of the leg, a feeling of swelling, cramps, restless legs, itching, and tingling (Bergan et al. 2006). In addition to the symptoms, varicose veins are usually considered to be cosmetically unappealing.

1.4.1.3 C₃: Oedema

Class C₃ venous disease is characterized by oedema. The consensus statement describes oedema as a perceptible increase in the volume of fluid in skin and subcutaneous tissue, characteristically indented with pressure (pitting oedema). The oedema may, however, become more resilient to palpation if it has lasted for a long time. Venous oedema usually occurs in the ankle region but may extend to the leg and foot, though usually the forefoot is spared (Eberhardt and Raffetto 2014).

Increased venous pressure in venous insufficiency is resisted by the microcirculation, but in CVI the defence mechanics are overwhelmed, and the capillary bed is filled, leading to an increase in the intracapillary pressure. Lymphatic capillaries and venules form a drainage system, but when the interstitial tissue is flooded, the drainage system can no longer compensate, and venous oedema develops (Allegra and Carlizza 2000). In the study conducted in Tecumseh, Michigan, oedema was present in approximately 10% of men and 20% of women with varicose veins (Coon et al. 1973). Not all oedema, of course, is due to CVI: in the San Diego Population study, 26.4% of oedematous legs had normal venous function and represented other causes besides venous. In the same study, nevertheless, oedema was closely associated with trophic changes and its probability was higher with superficial or deep venous disease (Criqui et al. 2003).

1.4.1.4 C₄: Skin changes

In the revision of the CEAP classification, category C₄ was further divided in two subcategories. C_{4a} comprises pigmentation and/or eczema, and C_{4b} lipodermatosclerosis (LDS) or atrophie blanche. Pigmentation is described as brownish darkening of the skin, usually occurring in the ankle region, but it may extend to the leg and foot. The definition of eczema in the statement is erythematous dermatitis that can lead to blistering, weeping or a scaling eruption of the leg skin, and it is most often located near varicose veins. LDS is a localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg, and it can sometimes involve the Achilles tendon, causing scarring or contraction. Atrophie blanche is a localized, usually circular whitish atrophic skin area that is surrounded by dilated capillaries and frequently hyperpigmentation; sometimes, healed ulcers may have a similar presentation, but they should not be mistaken for an atrophie blanche. Both LDS and atrophie blanche are signs of severe venous insufficiency, hence the need for the C_{4b} subcategory.

Eczema in CVI is often a part of stasis dermatitis, characterized by poorly demarcated erythematous and eczematous patches in the lower legs, often in combination with scaling and lichenification (Sundaresan et al. 2017). Occasionally, though, patients present with a plain persistent eczema in combination with varicose veins. Patients with CVI are susceptible to irritant contact dermatitis and can also become sensitized to topically applied medication, causing allergic contact disease (Barron et al. 2007).

Pigmentation in CVI is caused by the deposition of hemosiderin in the tissues. Venous pressure causes some red blood cells to extravasate and be disintegrated; hemosiderin is formed as a break-down product of haemoglobin. The dermal changes include extravasated erythrocytes, hemosiderin-laden macrophages, perivascular lymphocytic infiltration, dermal fibrosis and a proliferation of dilated small blood vessels in the papillary dermis (Sundaresan et al. 2017). In a study conducted in Brazil, the prevalence of hyperpigmentation was 5.7% in patients with varicose veins but no active or healed ulcers (Maffei et al. 1986). Pigmentation is often a part of stasis dermatitis.

Atrophie blanche (AB) has been described in 9–38% of patients with CVI, and it affects women more often than men. There are several theories on its underlying pathology, but impaired fibrinolysis and a local dysregulation of coagulation are probably the most important factors. Histologically, AB is characterized by a thin, flattened epidermis and dilated, tortuous capillaries in the superficial epidermis. Patients with AB can develop painful, often recurring leg ulcers (Maessen-Visch et al. 1999).

LDS can occasionally be preceded by an acute presentation of symptoms sometimes referred to as hypodermatitis or an acute phase of LDS: painful, poorly demarcated red to purple plaques in the lower leg with the affected areas warm to

the touch and very tender. This is often mistaken for cellulitis. In chronic LDS, the skin tightens and thickens in the ankle area and is hyperpigmented, giving the classic appearance of an “inverted champagne bottle” (Miteva et al. 2010). LDS predisposes to ulceration, and ulcers were present in 13% of patients with LDS a study conducted at the Mayo Clinic. It was also found that LDS was more common in females (87% of patients) and most of the studied patients, 85%, were overweight or obese (BMI over 34, 66%) (Bruce et al. 2002). Not much is known of the histopathology of LDS, since it is inadvisable to biopsy areas with LDS, for the biopsy wounds might not heal. Still, the little that is known is that there is pronounced membranocystic fat necrosis, septal fibrosis, haemorrhaging and hemosiderin deposition, as well as mononuclear inflammatory infiltrate and fibrotic, dense stroma. The pathogenesis is thought to involve abnormal fibrinolysis, leading to microthrombi and tissue hypoxia. Inflammation leads to activated white blood cells, and together with tissue hypoxia, they lead to elevated levels of transforming growth factor β 1 (TGF- β 1). This growth factor causes fibroblasts to express procollagen 1, generating skin hardening and fibrosis (Miteva et al. 2010).

1.4.1.5 C₅ and C₆: healed and active venous ulcer

The class C₅ comprises a healed venous ulcer and correspondingly, C₆ entails an active, open venous ulcer. Venous ulcers have a prevalence of roughly 1% (Ruckley et al. 2002). They are slow to heal: the mean duration is 9 months, and despite treatment, 20% remain present. Recurrence is also common, occurring in up to 67% of the cases (Callam et al. 1987).

The ulcer-predisposing mechanisms of venous ulceration are essentially the same as for the trophic skin changes, described above. Venous pressure causes the extravasation of red blood cells, creating an injury stimulus and activating white blood cells; in response to the iron overload in the tissue, the white blood cells secrete TGF- β 1. This decreases fibroblast proliferation and increases dermal tension, contributing to ulcer formation (Crawford et al. 2017).

1.4.2 Complications of varicose veins

The most common clinical presentations of venous disease have been described above. There are two important consequences of varicosities, however, that are not included in the CEAP classification but can cause significant health issues for the patient.

1.4.2.1 Thrombophlebitis

Superficial thrombophlebitis (STP) is an inflammation of the superficial veins combined with venous thrombosis. It is usually self-limiting and viewed as a trivial complaint by many patients and doctors alike, but it can be associated with DVT (deep venous thrombus) or PE (pulmonary embolism). Most often, thrombophlebitis occurs in the tributaries of GSV and can affect the whole GSV as

well; the second most common site is the SSV system (Leon et al. 2005). The incidence is unclear but probably higher than for DVT, which is one per 1,000 (Di Nisio et al. 2018). In a study conducted in France, the annual diagnosis rate was 0.64%, but patients with mild thrombophlebitis might not seek treatment. STP was associated with DVT or PE in 26.3% of the cases (Frappe et al. 2014).

The symptoms of STP include pain, erythema and swelling around a superficial vein. The affected vein is hard and cord-like upon palpation. When it is confined to varicose tributaries, it is considered a complication of the disease, but saphenous trunk STP is often associated with abnormalities in coagulation, such as a deficiency in protein S or C or antithrombin III, and factor V Leiden. An association with active cancer is often mentioned, but this association is weak and based on only few studies (Leon et al. 2005). The diagnosis of STP should be confirmed by ultrasound, since a clinical examination only can underestimate the extent of STP, and the presence of concomitant DVT should be examined (Nasr and Scriven 2015).

The most substantial evidence in STP treatment is for a prophylactic dose of fondaparinux, administered subcutaneously for 45 days. Topical treatments can reduce the local symptoms, but there is no data on whether they can prevent DVT/PE (Di Nisio et al. 2018). In a randomized study, oral rivaroxaban was noninferior to fondaparinux in preventing DVT/PE and the progression of the STP, and it did not cause major bleeding (Beyer-Westendorf et al. 2017).

1.4.2.2 Haemorrhage due to ruptured varicose veins

Bleeding from varicose veins can be fatal. In a 10-year autopsy study, there were 8 deaths from haemorrhage due to a rupture of varicosities out of 10,686 autopsy cases (<0.01%). In two cases, the bleeding followed trauma (Byard and Gilbert 2007).

Venous bleeding can occur from either acute perforation of a dilated vein through the weakened skin layer or from a worsening of a previous venous ulcer, causing erosion of the underlying vein. Bleeding can be controlled easily with elevation and by applying compression or a tourniquet distal to the bleeding site (Serra et al. 2018). The patient should be referred to a vascular surgeon or phlebologist for further examination. Both the underlying reflux and the bleeding site should be treated. The bleeding site can be treated with an injection of a sclerosant, such as sodium tetradecyl sulphate, while the patient awaits surgical treatment of the varicose veins (Tretbar 1996).

1.4.3 Venous Clinical Severity Score

The Venous Clinical Severity Score (VCSS) was created to supplement the CEAP classification (Rutherford et al. 2000a). The CEAP is relatively static in that, for example, a class C₅ patient can never become C₀ even after the ulcer heals and the

venous insufficiency is treated. Therefore, it is a poor instrument for studying the results of interventions. In the VCSS, nine clinical characteristics of venous disease are graded from 0 to 3 (absent, mild, moderate, and severe), with specific criteria given. The use of compressive therapy is also graded, and together these form a 30-point maximum scale. In 2010, the VCSS was revised to clarify and simplify the classification, simplifying its use (Vasquez et al. 2010). The VCSS has been validated, it is reliable and correlates well with the CEAP classification (Meissner et al. 2002). It has some limitations and has been criticized for not including previous interventions or the involvement of one or both legs (Perrin et al. 2006). Even though VCSS is often used in venous studies, it is not used in everyday practice to guide treatment decisions or to document improvement after treatment.

In the revised VCSS, varicose veins that have a diameter of under 3 mm when examined in a standing position are not assigned points. The term “varicose vein” includes any subcutaneous saphenous veins, their tributaries or non-saphenous superficial leg veins. Telangiectasia and reticular veins are not included. Corona phlebectatica (ankle flare) is defined as more than five blue telangiectasias on the inner or outer edge of the foot. Corona phlebectatica is associated with CVI and perforator reflux but is not considered skin pigmentation; it is considered a mild change. The last clinical descriptor, the use of compression therapy, does not directly reflect the severity of the disease; however, the application of compression therapy is a measure of compliance with conservative measures and will generally lead to diminished symptoms or signs, therefore yielding a lower VCS score.

Symptom/finding	none: 0	mild: 1	moderate: 2	severe: 3
Pain (venous origin) or other discomfort (aching, heaviness, fatigue, soreness, burning)		Occasional pain or other discomfort (does not restrict regular daily activities)	Daily pain or other discomfort (interfering but not preventing regular daily activities)	Daily pain or discomfort (limits most regular daily activities)
Varicose veins "varicose" veins ≥ 3 mm in a standing position		Few: scattered (isolated branch varicosities or clusters) Also includes corona phlebatica (ankle flare)	Confined to the calf or thigh	Involves the calf and thigh
Venous oedema presumes venous origin		Limited to the foot and ankle area	Extends above the ankle but below the knee	Extends to the knee and above
Pigmentation presumes venous origin; does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to the perimalleolar area	Diffuse over the lower third of the calf	Wider distribution above the lower third of the calf
Inflammation More than just recent pigmentation (erythema, cellulitis, venous eczema, dermatitis)		Limited to the perimalleolar area	Diffuse over the lower third of the calf	Wider distribution above the lower third of the calf
Induration presumes venous origin of secondary skin and subcutaneous changes (chronic oedema with fibrosis, hypodermatitis); includes white atrophy (atrophie blanche) and lipodermatosclerosis		Limited to the perimalleolar area	Diffuse over the lower third of the calf	Wider distribution above the lower third of the calf
Active ulcer number	0	1	2	≥ 3
Active ulcer duration (longest site)	N/A	<3 months	>3 months but <1 year	Not healed for >1 year
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

Table 1. VCSS. Adapted from Vasquez, Rabe et al. 2010

1.4.4 Aberdeen Varicose Vein Questionnaire

The Aberdeen Varicose Vein Questionnaire (AVVQ), also known as AVVSS (Aberdeen Varicose Vein Severity Score), is a patient-reported outcome measure (PROM) designed specifically to measure the venous insufficiency -specific quality of life, first introduced in 1993. It is intended to be able to justify the treatment of venous disease and can measure the improvement in the quality of life after interventions (Garratt et al. 1993a, Garratt et al. 1996). In the AVVQ, the patient fills in a questionnaire with 12 check-box questions concerning the symptoms of venous disease and to what extent they interfere with daily activities – questions commonly used to assess patients with varicose veins. Also, patients are asked to draw their varicose veins on a drawing of a leg. To interpret the drawing a grid is placed on the picture and the affected grids are counted. Each check-box question is assigned a weighed score. The questionnaire regards both legs, and the maximum score is 100. The AVVQ score has been shown to correlate with both VCSS and CEAP scores and could therefore potentially be used to guide varicose vein referrals (Ward et al. 2013). The AVVQ has been extensively validated, and the test-retest reliability and responsiveness are good, but the questionnaire has been criticized for its construction: some regard the weighing of the questions as biased, as the whole questionnaire and scoring system was created by only two physicians (Aber et al. 2017). Other PROMs for vein disease exist, such as the Varicose Veins Symptoms Questionnaire (VVSymQ), Specific Quality-of-life and Outcome Response – Venous (SQOR-V), and VEINES-QOL/Sym. However, the AVVQ remains one of the most used, at least in measuring outcomes of varicose vein interventions. Furthermore, the AVVQ has been shown to correlate well with the SF-36®, a commonly used generic quality-of-life measurement tool (Garratt et al. 1996).

The AVVQ questionnaire contains the following items in addition to the drawing that represents the distribution of veins (adapted from Wittens et al. 2015):

1. Duration of pain
2. Duration of use of pain medication
3. Degree of ankle swelling
4. Use of compression stockings
5. Extent of itching
6. Presence of discoloration
7. Presence of eczema
8. Presence of ulcer(s)
9. Degree of concern for appearance
10. Influence on choice of clothes
11. Interference with work and household jobs
12. Interference with leisure.

1.5 Diagnosis of superficial venous disease

Beside a clinical examination, the cornerstone of diagnosis and treatment in venous disease is duplex Doppler ultrasound (DDUS). It has replaced hand-held Doppler evaluation, which is less reliable and accurate and gives no morphologic information of the venous system (de Palma et al. 1993, Rautio et al. 2002). With ultrasound, the anatomy and function of the venous system can be evaluated at the same time.

Other diagnostic tools include plethysmography and phlebography. Their use in clinical practice has declined considerably after the advent of DDUS.

1.5.1. Duplex doppler ultrasound examination

The Union Internationale de Phlébologie (UIP) has released three consensus documents (the basic principles, anatomy and examination after treatment for varicose veins) concerning the duplex Doppler investigation of veins in CVI, describing the most important practices of the ultrasound evaluation (Coleridge-Smith et al. 2006, Cavezzi et al. 2006, De Maeseneer et al. 2011). The evaluation of superficial veins is performed with the patient standing, with the examined leg first in external rotation, heel on the ground and weight on the opposing limb. The room and ultrasound gel should be warm enough, since cold causes vasoconstriction. A high-frequency linear ultrasound transducer is used for vein scanning in the leg. The settings of the ultrasound machine should be appropriate: in the B mode, the lumen of the vein should be dark in the absence of a thrombus or stasis, the focal point should be set at the vein lumen or deeper, and for colour Doppler, low-flow settings ought to be used (Garcia and Labropoulos 2018).

Reflux – the most important finding in venous disease – is defined as a retrograde flow of blood lasting longer than 500 ms for superficial and deep veins; however, for femoral and popliteal veins, the cut-off value is 1,000 ms (Labropoulos et al. 2003, Wittens et al. 2015). Reflux is usually detected with colour flow and Doppler: the blue and red colours represent flow towards (retrograde) or away (antegrade) from the transducer, and velocities below the baseline represent antegrade flow, whereas velocities above the baseline represent retrograde flow. To create a pressure gradient that is necessary for the assessment of reflux, the calf is either compressed – preferably by a pneumatic tourniquet, since manual compression is not as reliable – or a Valsalva manoeuvre (especially for the FCV) is performed. Possible reflux can then be seen upon the release or diastolic phase. The highest repeatability for reflux detection is achieved in the morning, in the standing position and with the same provoking manoeuvre (i.e. tourniquet compression) (Lurie et al. 2012).

The DDUS examination is initiated from the groin. First, the SFJ is located with a transverse view. The terminal and preterminal valves of the GSV can be visualised. The AASV can be seen slightly external and lateral to the GSV. If there is reflux at the SFJ, it can be seen in continuity with the GSV and/or the AASV. The GSV is followed all the way down to the malleolar level, and its diameter is measured at a minimum of three points: a few centimetres below the SFJ, at the middle or distal thigh and at the proximal calf. The vein is scanned for reflux with colour Doppler, and the depth of the vein from the skin is noted. If the vein becomes superficial and/or tortuous, the length of the straight section is noted, since it affects the choice of treatment. Similarly, the accessory saphenous veins, especially the AASV, may be examined. However, if there is substantial reflux in the GSV, it may conceal a more minor reflux in the AASV in the initial DDUS examination (Anwar et al. 2019). The CFV is scanned for retrograde flow both below and over the SFJ. The presence of phasic flow during respiration and the presence of reflux are noted. The SSV and popliteal vein are then examined with the patient facing away but with the leg similarly relaxed as before. Any reflux at the SPJ is noted, and the SSV is traced similarly as the GSV. The SSV may also extend cranially in the thigh; this extension is also examined for reflux. The popliteal vein is also investigated for reflux. Calf perforators may likewise be visualized and scanned for reflux, but not all of them can be detected by ultrasound. There is no consensus on the significance of bidirectional flow in the perforator veins, and for most patients, perforators are not the source of reflux nor in need of treatment, with the exception of those with either C5 or C6 disease (Recek 2016).

1.5.2 Plethysmography

Plethysmography measures the changes in volume within the leg. In air plethysmography, the limb is enclosed in a rigid jacket (plethysmographic chamber) filled with air. The changes in leg volume as a result of emptying or filling veins produce changes in the chamber, which is connected to a volume recorder. The venous filling time (VFT) is the time it takes for the antigravitational mechanisms in the leg to fail. In subjects with venous insufficiency, the filling is faster and the VFT correspondingly longer. The VFT is usually measured by first emptying the leg veins with calf muscle action and then measuring the time it takes to achieve the starting leg volume. The VFT reflects the severity of the venous disease. It has been shown to correlate well with the GSV reflux time (Lattimer et al. 2014).

Strain-gauge plethysmography was first described in 1953 as a diagnostic tool. It measures the changes in volume indirectly, by determining changes in limb dimensions using strain gauges (Whitney 1953). It can distinguish the superficial and deep venous components of CVI (Skeik et al. 2012).

In photoplethysmography, a photoelectric transducer is attached above the ankle, and the patient is asked to perform dorsiflexion of the ankle several times (while

sitting); the examination can also be performed while standing. A normal VFT is longer than 20 seconds; shorter than 15 seconds indicates venous insufficiency. In such a case, a tourniquet is placed on the leg to stop the outflow of the GSV and the procedure is repeated, and if the VFT is normalized, it is the GSV that is insufficient (Fronek 1995).

Plethysmography methods are fast and performer-independent investigation tools and can provide information about deep venous involvement in the CVI. However, they do not provide information about the anatomy of the venous system, and a DDUS examination is required for selecting the appropriate treatment. They also require equipment not readily available in many clinics. In practice, they no longer have a role in venous insufficiency diagnostics.

1.5.3 Phlebography

Phlebography is an invasive method of venous examination. It involves an injection of contrast medium to the inspected veins and the subsequent monitoring of its flow with fluoroscopy. Previously, before the advent of DDUS, acute venous thrombosis was diagnosed with phlebography, in addition to studying reflux. In the lower limbs, phlebography can be performed in either an ascending or a descending manner. Ascending phlebography is performed on a tilting table positioned at 30–65 degrees from the horizontal level, with feet down. In order to study the superficial veins, tourniquets are used to block the superficial system. A vein at the dorsum of the foot is then cannulated and contrast medium injected slowly. Films are then taken to track the speed and pattern of the blood flow in the veins (Greitz 1954, Thomas 1990). Descending phlebography visualises GSV reflux and deep venous reflux well (Thomas 1990). In descending phlebography, a catheter is inserted into the CFV by the Seldinger technique. The patient is placed upright on the tilting table, and the flow of contrast medium is inspected during both normal breathing and a sustained Valsalva manoeuvre to detect reflux (Kistner and Kamida 1995). Varicography is a method in which contrast medium is injected directly into the varicose veins and the patient is tilted from a foot-down position first to a horizontal and then to a head-down position to trace the venous filling with fluoroscopy (Thomas 1990).

At present, phlebography is usually performed in the case of a suspicion of a deep venous problem. Its value in chronic venous disease is not so much diagnostic but rather therapeutic, since both stenting of a deep venous obstruction (usually in the iliac veins) and blocking of pelvic sources of reflux (in ovarian or testicular veins) can be achieved endovenously.

2 TREATMENT OF SUPERFICIAL VENOUS INSUFFICIENCY

As previously mentioned, the GSV is the most common source of reflux in superficial venous insufficiency (Maurins et al. 2008). Because of this, most published works study its treatment, and it is the focus of this review.

2.1 Compression therapy

2.1.1 Compression therapy: history and overview

Early on, Hippocrates (465-375 BCE) recognized the relationship of varicose veins and leg ulcers, and recommended compression treatment with two layers of bandages. A few centuries later, Celsus also proposed a kind of compression therapy using plasters and thin linen roller bandages. Wiseman (1662-1676) devised a laced compression stocking which he successfully used to treat venous ulcers. This was the precursor for modern compression hosiery that are still important in the treatment of venous disease (Royle and Somjen 2007).

Compression decreases capillary filtration and enhances lymph flow as well as reduces venous reflux. Compression treatment reduces symptoms of venous disease such as swelling, local variceal pain and diffuse leg pain (Raju et al. 2016).

Compression stockings are most often of below the knee length, but thigh length or full stockings can also be used. The stockings are classified according to the interface pressure they create: class I (low compression) provides compression of 18-21 mmHg, class II (moderate) 23-32 mmHg, class III (high) 34-46 mmHg and class IV (very high) 49 mmHg or higher (Partsch et al. 2008). For varicose veins or SVT, class I-II stockings are usually prescribed. The term 'conservative treatment' in venous disease usually refers to compression treatment.

2.1.2 Compression therapy: complications

Not many complications of compression hosiery are described in literature. The complaints described are somewhat minor, but commonly associate with poor compliance; they include discomfort, dry skin, difficulty donning stockings, tightness, feeling hot, skin irritation, pain and lack of cosmetic appeal (Kankam et al. 2018). Many of these issues can be resolved with correct selection of compression hosiery type and material.

The most feared complication of compression treatment is ischaemia, caused by the reduction of the cutaneous blood flow with external compression. Reports of gangrene and ulcers developed during compression treatment have been published (Merrett and Hanel 1993). Many patients with venous leg ulcers also have peripheral arterial occlusive disease (PAOD), with incidence for both of these conditions increasing by age (Ladwig et al. 2014). The extent of PAOD can be quite reliably measured with ankle-brachial pressure index (ABPI): normal ABPI is over 0.9, and it is widely accepted that values ≤ 0.5 represent severe ischaemia and are contraindication for compression therapy (Weller et al. 2019). However, the question remains, how much pressure patients with ABPI of 0.5 to 0.8 can tolerate. Schuren et al. conducted a study measuring the compression created by compression bandages and showed that even patients with ABPI as low as 0.5 to 0.6 tolerated 30–40 mmHg pressures well (Schuren et al. 2010). Compression systems adapted to PAOD have been created; they administer a low resting pressure but an effective working pressure. Using one of these systems it was demonstrated that patients with ABPI between 0.5 and 0.8 can well endure a compression of on average 32 mmHg, with no skin damage or hypoxia-related pain (Ladwig et al. 2014). Sometimes, especially in patients with diabetes mellitus, the ABPI is over 1.2. This signifies that the arteries are calcified to the extent that they cannot be compressed, and the measurement is therefore not reliable; the toe pressures could in these cases provide better information on the sufficiency of arterial blood flow (Weller et al. 2019). In summary, the evidence of a certain cut-off value of ABPI in compression treatment is lacking. According to an international consensus statement, it is recommended to check the foot and ankle pulses before initiating compression therapy, and if the pulse is weak or absent, ABPI should be measured. If the ankle or toe pressure is low, inelastic compression binding is better tolerated than a graded compression stocking. The effect of the compression on the blood supply of the leg should be monitored in every patient with ABPI less than 0.9 (Rabe et al. 2020).

2.1.3 Compression therapy: results

According to a Cochrane systematic review, the evidence on compression stockings as the sole or initial treatment of varicose veins without venous ulcers is lacking (Shingler et al. 2013). Similar conclusion was attained by a previous review (Palfreyman and Michaels 2009). After these reviews, however, the results of a randomized controlled trial (RCT) comparing compression treatment with surgery for varicose veins was published. In the study, patients who underwent surgery had better VCSS and quality of life compared to those in compression group after two years of follow-up. After the end of the follow-up period, many patients in the compression treatment group sought interventional treatment (Sell et al. 2014).

Based on studies, venous ulcers are 2–4-fold more likely to heal with compressive bandages compared to non-compressive bandages. However, compression

stockings are not often used by patients even when prescribed, since they are frequently experienced uncomfortable. Poor compliance is a major flaw of the compression treatment in both studies and real life. According to a study by Raju et al., only 21% of CVD patients used the stockings daily. Some of the reasons given for not using the stocking were ineffectiveness (15%), a feel of binding, cutting of circulation or poor fit (13%), hotness (7%), soreness (2%), and aggravating, itching and dermatitis (2%) (Raju et al. 2016). A systematic review reported that some 66% of patients enrolled in venous studies had good compliance with compression stockings; the compliance seemed to be higher if the prescribed compression was \leq 25 mmHg (Kankam et al. 2018). It is recommended to check the pressure level, material, fitting and correct donning and doffing of the compression garments if the patient reports discomfort or pain (Rabe et al. 2020).

In pregnant women, blood volume and venous distensibility and capacity are increased, and the growing womb constitutes a mechanical obstruction that hampers venous return from the legs. These changes lead to venous symptoms and signs that can be alleviated with compression. Büchtemann et al. found that if women wore compression stockings from the 20th week after gestation onward, their venous pump function and refilling time did not deteriorate, in contrast to those not wearing stockings (Buchtemann et al. 1999). Similarly, graduated compression was found to increase venous emptying in pregnant women (Nilsson et al. 1992, Austrell et al. 1995). Despite this, there is no evidence that stockings prevent varicose veins during pregnancy (Thaler et al. 2001).

Nonetheless, in the Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) for Management of Chronic Venous Disease is stated that elastic stockings are recommended as an effective treatment modality for symptoms and signs of chronic venous disease, and temporary use of them may be considered in patients with CVI awaiting further investigation and as a definite treatment in those patients not managed by invasive methods (Wittens et al. 2015). The National Institute for Health and Care Excellence (NICE) guidelines, used in the UK, specify that compression hosiery should not be offered as a treatment for varicose veins unless interventional treatment is unsuitable (Marsden et al. 2013).

2.2 Open surgery

2.2.1 Open surgery: history and overview

Surgery for varicose veins dates back to before the Common Era. Phlebectomies – the removal of varicose veins through small incisions – were described as early as in the first century CE (van den Bremer and Moll 2010). Paul of Aegina recounted the ligation and removal of the GSV in the Byzantine era (Lascaratatos et al. 2001). The technique was introduced to the Western medical community by Trendelenburg,

who ligated the GSV at the junction of the middle and lower thirds of the thigh to eliminate reflux (Trendelenburg 1890). Moore modified his technique and wrote a paper on the high ligation of the GSV under local anaesthesia with cocaine as day surgery, reporting remarkable success in healing venous ulcers. He stressed the importance of ligating the GSV above its branches from a transverse groin incision (Moore 1896). The contemporary open surgical technique of treating an insufficient, refluxing GSV involves both high ligation, as described by Moore, and the stripping (removal) of the GSV. The first stripping instrument was introduced in 1905, and Babcock developed the flexible internal saphenous stripping device a few years later: essentially, a similar device is used today (van den Bremer and Moll 2010). This operation entailing high ligation and stripping has for long been the benchmark of superficial venous surgery.

Open surgery of the GSV is traditionally performed under either general or spinal anaesthesia. The high ligation of the GSV is performed through a small transverse groin incision. The importance of stripping the GSV has been confirmed by many studies. Sarin et al. randomized 56 limbs to high ligation (HL) only and 49 to high ligation and stripping (HL+S); at three months, significantly more residual GSV reflux was seen with DDUS in the ligation only-group (Sarin et al. 1992). In 1994, Sarin reported the 21-month follow-up of the study: recurrence was found in 65% of the patients who had undergone HL only, in contrast to 17% in the HL+S group (Sarin et al. 1994). Jones et al. described the two-year follow-up of a similar study setting, with recurrence rates of 43% in the HL group and 25% in the HL+S group (Jones et al. 1996). The five-year results of an RCT studying recurrence were published in 1999, reporting that in the HL group, some 48% of the patients remained asymptomatic and satisfied with the results, while the corresponding figure in the HL+S group was 61% (Dwerryhouse et al. 1999). In the 11-year follow-up of the same study, it was discovered that many patients develop recurrence in spite of HL+S, but the need for additional surgery was lower in the HL+S than the HL group even in the long run (Winterborn et al. 2004).

The GSV is usually stripped to the knee level or just below because, in the lower leg, the GSV is intimately connected with the saphenous nerve that can be injured if the stripping is extended to the ankle level; limiting the length of the stripping does not, according to one study, increase recurrence (Holme et al. 1996). Phlebectomies – the removal of varicose veins through small incisions – can be performed concomitantly with the HL+S procedure.

2.2.2 Open surgery: complications

Open surgery is not without complications (*Table 2* on page 66). Minor complications, such as wound infections, bleeding and neurological complications are relatively common whereas more severe complications, such as major vessel injuries and thromboembolic events like DVT and PE are quite rare (de Mik et al.

2019). In a retrospective analysis of 599 patients (973 limbs) treated with open surgery (including the high ligation of the GSV, the ligation of the SSV, and phlebectomies), 4% developed wound complications and 10.7% had minor neurological disturbances. Major complications (such as DVT, PE, major nerve injury and vessel injury) were reported in 5 patients (0.83%) (Critchley et al. 1997). In a retrospective study of 997 patients who underwent varicose vein surgery, six major in-hospital complications were encountered among the 272 patients in the HL+S group, and 16 patients treated with HL+S were readmitted within 30 days for surgery. Of these 16 patients, six had either a DVT or a PE; compression bandages were introduced during the study period, and their use was reported to reduce the incidence of thromboembolic complications (Miller et al. 1996). The reported small number of thromboembolic complications may be explained by studies only reporting symptomatic cases. In contrast, a prospective study conducted by van Rij et al. reported DVT in 5.3% of patients after HL+S; less than half were symptomatic (van Rij et al. 2004). Ahmed et al. reported DVT in 1.79% of patients in a follow-up ultrasound scan after open surgery for GSV; no PE's were encountered (Ahmed et al. 2018). One study concluded that clinically significant DVT's after open surgery present as leg swelling, and that routine ultrasound scan is therefore unnecessary: none of the patients without early clinical signs subsequently developed a clinical DVT (Bhogal and Nyamekye 2008).

According to the study by Holme et al., up to 29% of the patients who had undergone high ligation with stripping suffered a permanent saphenous nerve injury in contrast to only 5% of those with partial (thigh part) stripping of the vein (Holme et al. 1996). This is explained by the anatomy: the saphenous vein runs deep to the GSV in the thigh and becomes progressively more superficial at around the knee, coming into close contact with the GSV usually at 2–3 centimetres below the level of the tibial tuberosity. Saphenous nerve injury commonly presents as paraesthesia at the medial ankle, for most patients a minor concern, but can also cause persisting dysesthesia that is difficult to treat (Sam et al. 2004). The stripping technique can affect the rate of nerve injury; the smallest percentage of persistent saphenous nerve injury has been reported in distal stripping with invagination (Jaworucka-Kaczorowska et al. 2015). In a retrospective study, Morrison detected saphenous nerve deficits by neurological examination in 58% of legs previously treated with high ligation and stripping to the ankle; most patients were unaware of the deficit before the examination. However, 13.3% reported burning or shooting pain at some point after the operation (C. Morrison and Dalsing 2003). Wood et al. conducted a prospective study of nerve injury after HL and stripping to below the knee. At six weeks, 15.6% of patients had sensory deficits consistent with saphenous nerve injury, and at 12 months, 8% had persistent deficits. Two patients regretted having had the operation (Wood et al. 2005).

Wound infection rate after HL+S is, according to a meta-analysis, 1.9%. Bleeding and haematoma occur in 4.8% (Pan et al. 2014). The incidence of major vessel

injury has been recorded to be from 0.017% to 0.017% (Critchley et al. 1997, Frings et al. 2001).

Open surgery for GSV insufficiency is most commonly done under general or spinal anaesthesia, both of which have their own risks. The mortality related to anaesthesia has decreased over the past five decades (Bainbridge et al. 2012). General anaesthesia complications include cardiovascular complications such as myocardial infarction, heart failure and cardiac arrest; respiratory complications such as aspiration; postoperative cognitive dysfunction, dental damage and drug reactions are also known adverse effects (Harris and Chung 2013). Serious complications of spinal anaesthesia are fortunately rare; according to a Finnish study, the risk is 1:35,000 (Pitkanen et al. 2013).

2.2.3 Open surgery: results

In the REACTIV trial, an RCT comparing open surgery to conservative treatment for varicose veins, it was found that surgical treatment produced better results in terms of symptomatic relief, patient satisfaction and quality of life. The cost-effectiveness ratio per QALY (quality-adjusted life-year) was also greater with surgery than with conservative treatment (Michaels et al. 2006). The ESCHAR study compared HL+S with compression therapy in patients with venous ulcers. It was observed that, while initial ulcer healing rates were similar, the 12-month ulcer recurrence rate was significantly reduced in the surgery group (Barwell et al. 2004).

One of the drawbacks of open surgery is its high recurrence rate. Up to 70% of patients have some degree of varicose vein recurrence at ten years after surgery (Campbell et al. 2003). Previously, many authors blamed technical errors – namely failure in adequately dissecting the SFJ and ligating all side branches – for the recurrence at the groin, but Nyamekye and colleagues showed that most of the recurrence at the SFJ is due to neovascularization (Nyamekye et al. 1998). Neovascularization refers to the formation of new, usually tortuous veins typically at the site of saphenous vein ligation (Wittens et al. 2015). In patients treated with either HL or HL+S, it is the most common source of recurrence. If treated with HL only, neovascularization can connect the SFJ with the intact GSV (Dwerryhouse et al. 1999). Allegra et al. recorded the pattern of recurrence in surgically treated patients at five years, and found that some 12.6% had recurrence originating from the SFJ (Allegra et al. 2007). Kostas et al. detected reflux in 42 out of 113 limbs on which open surgery had been performed 5 years earlier. In 15%, this was considered to be due to disease progression, and in 11.5% the reflux resulted from neovascularization. Tactical or technical errors were responsible for 9.7% of the recurrence (Kostas et al. 2004). Strip-tract revascularization accounts for a high proportion of recurrence as well: five to eight years after ultrasound-guided HL+S, some strip-tract revascularization was demonstrated in up to 82% of patients, and 12% presented with total revascularization and reflux of the stripped GSV (Ostler et

al. 2015). Winterborn et al. followed up patients treated with either HL or HL+S for 11 years, concluding that some 62% had developed clinically significant recurrent varicose veins. The presence of neovascularization increased during the follow-up period from 36% at three years to 65% at 11 years (Winterborn et al. 2004).

2.3 Foam sclerotherapy

2.3.1 Foam sclerotherapy: history and overview

Foam sclerotherapy is a minimally invasive treatment for varicose veins. In sclerotherapy, the sclerosant is injected directly into the veins in either liquid form or as foam. The objective of sclerotherapy is to disrupt the vein wall by causing an inflammatory response (Albanese and Kondo 2010). The vein spasms and is thrombosed as a result, and, if successfully treated, the vein subsequently atrophies.

The first attempts at sclerotherapy were performed in the 1860s after the invention of the hypodermic needle (van den Bremer and Moll 2010). The results were not great: the treated segment usually recanalized within a few months, and the treatment sometimes caused extensive thrombosis (Fegan 1963). Hence, sclerotherapy was all but abandoned for a time. In the early 20th century, however, it again gained popularity. In the 1940s, the method of creating foam to intensify the contact between the endothelium lining of the vein and the sclerosant was developed (Wollmann 2004). Fegan popularized the method in his article published in *Lancet* in 1963, describing the procedure in great detail (Alder and Lees 2015, Fegan 1963). There seems to be an ebb and flow to the popularity of sclerotherapy, since the use of it became more limited again in the 1970s due to its poorer long-time results compared to surgery (van den Bremer and Moll 2010). After the advent of duplex ultrasound, sclerotherapy became more targeted, and in the 21st century, the Tessari method was invented, enabling a stable, dense and consistent foam to be easily created (Tessari et al. 2001). This led sclerotherapy to resurface as an excellent treatment method.

Presently, foam sclerotherapy is usually performed under ultrasound guidance (ultrasound-guided foam sclerotherapy, UGFS). Telangiectasia and other small veins can be treated with liquid sclerotherapy by sight. In UGFS, the foam is usually produced by mixing a sclerosant with air in a ratio of 1:3–1:4 using the Tessari method utilising two syringes and a stopcock. The most common sclerosants used include sodium tetradecyl sulphate (STS) and polidocanol in concentrations of 1% or 3%. The resulting foam is injected into the treated vein segment through cannulas or butterfly needles, and the induced spasm and the flow of the foam is monitored with ultrasound. To prevent thrombotic complications, the recommended maximum volume of foam injected in one session is 10 ml (Rabe et

al. 2014). This limits the use of UGFS; for example, large varicosities cannot be treated at one sitting. After the treatment, a compression stocking is often applied to be used daily for up to two weeks; some operators even use rolls of bandage over the treated veins under the stocking to generate further compression (Alder and Lees 2015). On the other hand, it has been shown that not using compression stocking after UGFS did not result in inferior results in 28-day follow-up and that compression stockings did not prevent side effects (Hamel-Desnos et al. 2010). UGFS can be performed at an outpatient clinic, and no sick leave is usually required (*Table 2* on page 66).

2.3.2 Foam sclerotherapy: complications

The possible and significant complications of UGFS include SVT, DVT, stroke, tissue necrosis, anaphylaxis and nerve injury. Cosmetic complaints comprise pigmentation and telangiectatic matting. Anaphylactic reactions are fortunately very rare. The incidence of DVT after UGFS is reported to be low; according to one study reporting the results of almost 40,000 sclerotherapy procedures, it was 0.57% per procedure or 0.82% per patient (O'Donnell et al. 2015). However, many DVTs can be silent. In a study where patients were systemically examined for DVT after UGFS, the incidence was 1.8% (Bergan et al. 2006). Kulkarni et al. reported an incidence of 1.5% for DVT in 1000 legs treated with UGFS (Kulkarni et al. 2013). Myers and Jolley similarly scanned 852 patients after UGFS treatment, finding a DVT in 1.5%, asymptomatic in all cases. The risk of DVT was more than three times greater if the volume of injected foam is over 10 ml or if the treated vein diameter was over 5 mm (Myers and Jolley 2008).

One of the most feared complications is stroke. Not many published case reports of stroke after UGFS exist, and, happily, most of the patients recovered with no long-term sequelae. The presence of a right-to-left shunt in the heart, usually a patent foramen ovale (PFO), is the most consistent risk factor; PFO is therefore considered a contraindication for UGFS (Parsi 2012). The minor neurological complications include visual disturbances, and they can occur in up to 1.4% of the patients (Jia et al. 2007). Skin necrosis is a rare complication with an incidence of less than 0.1% (Gillet et al. 2014). The most common reason for necrosis is arterial occlusion, often following an inadvertent arterial injection. Nerve damage is rare and often transient (Cavezzi and Parsi 2012). Telangiectatic matting occurs in 15–20% patients, usually resolving spontaneously within one year. Hyperpigmentation of the skin over the treated varicosities is common, seen in up to 10–30% of the patients, and, similarly, it also has a tendency to dissipate (Goldman et al. 1995). The median incidence of SVT was 4.4% in a systematic review (Jia et al. 2007). However, it is sometimes difficult to distinguish venous sclerosis and thrombosis from thrombophlebitis, and the incidence of SVT may therefore be under-reported (Cavezzi and Parsi 2012). Compared to open surgery, UGFS generates less complications (*Table 2* on page 66).

2.3.3 Foam sclerotherapy: results

The most important reason for why UGFS is no longer a popular modality in the treatment of saphenous trunks is its high tendency for recurrence. An accurately comparison of the results of UGFS between studies is, however, rather difficult because the treatment is not standardized: the sclerosant, air-to-sclerosant ratio, injection sites, number of succeeding treatments, etc., vary from one operator and clinic to another. The reflux rate has been shown to be greater in the UGFS group compared to the surgery group at two years: 35.0% vs. 21.0%, respectively (Shadid et al. 2012). In a randomized clinical trial comparing UGFS with surgery and endovenous laser ablation (EVLA), the treated GSV was obliterated in 23% of the patients in the UGFS group compared to 85% in the surgery group at five years. During the follow-up, 32% of the legs treated initially with UGFS needed one or more reinterventions (van der Velden et al. 2015a). In another trial, the five-year GSV occlusion rate was also significantly poorer in the UGFS group than in the HL+S or endovenous thermal ablation group, and the need for a reintervention was greater (Lawaetz et al. 2017a). The five-year results of the CLASS (Comparison of Laser, Surgery, and Foam Sclerotherapy) study show that the quality of life at five years is better after surgery or EVLA than after UGFS. The GSV occlusion/obliteration rate was 33.3% for UGFS (Brittenden et al. 2019).

In a prospective series following patients who underwent treatment for GSV reflux treated with UGFS, 43% required additional UGFS treatment between six weeks and six months, and 23% between six months and twelve months; between one and two years, 16.5% of the patients received additional treatment, after which point, the rate was 6.7–8.8% annually until five years. The clinical results were reported as excellent, and patient satisfaction was apparently high (Chapman-Smith and Browne 2009). In 2012, Kalodiki et al. published the five-year follow-up of a study comparing UGFS in combination with HL to traditional HL+S. At five years, the obliteration or occlusion rate of the GSV was similar in both groups; however, in the UGFS+HL group, additional UGFS treatments had been performed, if necessary. The disease-specific quality of life, as measured with the AVVQ, was significantly better in the HL+S group. It was proposed that UGFS could be offered “like dental care”, treating over and over again when the problem reappears (Kalodiki et al. 2012).

The cost-effectiveness of UGFS has also been studied. In a recent analysis, UGFS had the lowest cost over 5 years when compared with other endovenous ablation techniques and surgery, but it was also regarded as the least effective (Epstein et al. 2018). Of late, the five-year results of the CLASS study were published. The cost-effectiveness calculations favoured either EVLA or surgery over UGFS, depending on the type of analysis (Brittenden et al. 2019).

The Clinical Practice Guidelines of the ESVS for the Management of Chronic Venous Disease state that UGFS has a higher recanalization rate when treating veins larger

than 5–7 mm in diameter, and it is not recommended as the first choice of treatment for saphenous vein incompetence. Also, repeat treatments are considered to be an element of UGFS, and the costs of this should be included in cost analysis (Wittens et al. 2015).

2.4 Radiofrequency ablation

2.4.1 Radiofrequency ablation: history and overview

Current treatment of GSV reflux is centred around endovenous treatment methods, and the Seldinger technique forms the basis for these. The Seldinger technique was invented by a Swedish radiologist, Sven-Ivar Seldinger, in 1953. In the technique, a needle is introduced into the vessel, a guide wire is pushed into it, and the needle is removed. The catheter is then guided in over the wire, which also is removed. Further instrumentation can then be advanced into the vessel easily through the catheter (Seldinger 1953). Endovenous treatment methods are less invasive than HL+S and can be performed in an outpatient setting using tumescent anaesthesia.

Radiofrequency energy was first used for the ablation of abnormal conduction pathways of the heart (van den Bremer and Moll 2010). The first account of treating varicose veins with radiofrequency was published in 1966 in the Polish Journal of Surgery (Politowski and Zelazny 1966). However, radiofrequency ablation (RFA) became usable only after the advent of tumescent anaesthesia. Tumescent anaesthesia delivers anaesthesia and vein compression in addition to protecting adjacent structures from heat energy, at the same time (Nyamekye 2019). In 1998, the first reports of RFA with a dedicated catheter were published (Lohr and Kulwicki 2010).

In RFA treatment of the GSV, a catheter with a heating element delivering radiofrequency energy is introduced into the vein with the Seldinger technique. The tip of the catheter is placed either just distally to the ostium of the superficial epigastric vein or a few centimetres below the SFJ. In most cases, the most proximal part of the GSV remains untreated (Lohr and Kulwicki 2010). At first, the vascular community was sceptical about the ideology behind endovascular ablation, since the ligation of GSV in the groin at a point above all tributaries was, according to the conventional perception, important in order to prevent recurrence (van den Bremer and Moll 2010). Through an ultrasound examination of patients who had undergone RFA ablation of the GSV two years earlier, it was shown that, even though the SFJ was patent with a short stump of a patent GSV serving as a conduit for physiologic flow from its proximal branches, the GSV trunk remained occluded or obliterated in most patients (Pichot et al. 2004).

The tumescent solution typically consists of a crystalloid solution containing local anaesthetic and often, but not always, epinephrine (Holt 2017). It is injected around

the GSV after catheter placement under ultrasound guidance, and as a result, the GSV is compressed around the RFA catheter. The currently most popular RFA catheter type allows segmental ablation, heating the vein wall to 120 °C conductively by a coil at the distal end for 20 seconds; thereafter, the catheter is pulled back for the length of the heating element and the treatment repeated, until the whole vein is ablated (Lohr and Kulwicki 2010). However, the method of catheter withdrawal is device-specific, and in some devices the energy is delivered continuously, requiring continuous withdrawal as well (Goodyear and Nyamekye 2015). RFA causes the denaturation of collagen in the vein wall; injury and inflammation of the vein wall lead to a fibrotic sealing of the vessel lumen. Also, endothelial denudation and swelling of the cellular components of the vein wall are seen (Zikorus and Mirizzi 2004). After treatment, a compression stocking is usually used for a couple of days. According to a recent review, an extended use (over two days) of compression after thermal ablation does not yield benefits, and the compliance rate may be poor. However, if phlebectomies are performed in addition to thermal ablation, a longer period of compression stocking use might be beneficial (Al Shakarchi et al. 2018). In contrast to UGFS, with thermal ablation, several venous segments such as both GSVs and SSVs can be treated in one session.

RFA and EVLA can be combined with concomitant phlebectomies or foam sclerotherapy for tributary varicosities. Alternatively, the treatment of varicosities can be delayed and, if necessary, performed with foam sclerotherapy in an outpatient setting later. It is debatable whether a simultaneous or staged procedure is the most advantageous. Some branch varicosities will diminish after treating the saphenous trunk, but some 30%–60% will require treatment (Hager et al. 2017). In the AVULS (Ambulatory varicosity avulsion later or synchronized) trial, patients undergoing endovenous thermal ablation were randomized to receive either simultaneous phlebectomies or delayed treatment with foam sclerotherapy. Many eligible patients refused to participate in this study, preferring a single-sitting treatment. In the delayed group, 36% of patients required additional treatment. The quality of life at six weeks was better in the simultaneous treatment group, and a small difference in favour of simultaneous treatment persisted throughout the follow-up period of one year. The VCSS scores were lower in the simultaneous treatment group for up to one year (Lane and Kelleher et al. 2015). However, the policy of concurrent RFA and phlebectomies seems to increase the risk of endovenous heat-induced thrombosis (described in detail below), although the pathological mechanism for this is unclear (Hicks et al. 2017).

2.4.2 Radiofrequency ablation: complications

One of the possible complications of RFA is endovenous heat-induced thrombosis (EHIT): the extension of the thrombus in the treated vein into the deep vein. EHIT can be classified into four categories: type 1 thrombosis extends to the superficial–deep junction, types 2–3 extend into the deep vein but do not occlude

it, and type 4 forms an occlusive vein thrombus (Kabnick 2005). EHIT usually resolves spontaneously within a short time, but it may also detach and cause a PE, or completely occlude the deep vein, thus resulting in a DVT. The ESVS guidelines advise the clinicians to use anticoagulation if the thrombus extends into the common femoral vein (Wittens et al. 2015). In a meta-analysis including 52 studies (16 398 patients), type 2–4 EHIT occurred in 1.4% of patients treated with thermal ablation. This review assessed RFA and EVLA as one group, but the results were similar when the RFA and EVLA groups were analysed separately. The incidence of PE was 0.1% and of DVT 0.3% (Healy et al. 2018). The rate of complications after RFA compared to other GSV treatment methods is presented in *Table 2* on page 66.

Nerve injuries may occur during thermal ablation. When treating the GSV, the nerve most susceptible to injury is the saphenous nerve, resulting in paraesthesia around the ankle. The incidence of paraesthesia after thermal ablation varies between studies, but it is reported to range from 4% to up to 26% (Hirsch 2017). Considering the anatomy, nerve injury is more common if the entry point of the catheter is at the ankle (Wozniak et al. 2016). To prevent thermal injury, a good tissue separation should be achieved, with at least 10 mm of clearance around the target vessel (Goodyear and Nyamekye 2015). In a publication on complications after thermal ablation, it was shown that first-generation RFA catheters caused significantly more paraesthesia than newer catheters (12% vs. 5.2%) (Dermody et al. 2013). Skin burns are a possible complication, but the incidence has dropped with the new, conventional radiofrequency machinery to 0%–2% (Goodyear and Nyamekye 2015). Skin burns and pigmentation can be avoided with an abundant use of tumescence and avoidance of treating very superficial veins (Anwar et al. 2012).

2.4.4 Radiofrequency ablation: results

The efficacy of RFA has been demonstrated in several randomized studies. In 2003, the results of the EVOLVEs study, a prospective multicentre randomized comparison of RFA vs HL+S in the treatment of GSV insufficiency, were published. The immediate success rate for RFA was 95% (there were two cases of technical error), and at four months, 90.5% of the treated GSVs were completely occluded. Compared to HL+S, RFA had fewer adverse effects, such as infections, ecchymoses and haematomas, and the patients returned to normal daily activities earlier. Paraesthesia was initially reported more frequently in the RFA group, but the difference between the groups was negligible at four months of follow-up (Lurie et al. 2003). During two-year follow-up, 51% of the GSV trunks treated with RFA shrunk in size, and 41% became completely undetectable by ultrasound. It was concluded that the results were at least equal to HL+S (Lurie et al. 2005). Another, although smaller, study was conducted in Finland, with 15 patients randomized to RFA and 13 to surgery. However, as the endovenous concept of leaving the SFJ intact was perhaps foreign at the time, HL was performed on all RFA patients as

well. In patients treated with RFA, the immediate GSV closure rate was 100%, and none of the veins recanalized during the three-year follow-up (Perala et al. 2005).

After these initial, promising results, other trials took place. Helmy ElKaffas et al. compared RFA with HL+S in a randomized study that recruited 180 patients and followed them for up to two years. The immediate occlusion rate was 94.5% in the RFA group, and those in whom the treatment was unsuccessful underwent concomitant HL+S. The incidence of postoperative complications was significantly lower in the RFA group, and the recurrence rates at two years were similar in both groups (Helmy ElKaffas et al. 2011). In another study with a similar setting, the immediate advantages of RFA were evident, with patients returning to work earlier and having considerably less pain as well as a higher quality of life after the procedure. In this study, all RFA-treated GSVs were occluded at five weeks (Subramonia and Lees 2010). In a landmark study from Denmark, patients were randomised to undergo either EVLA, RFA, UGFS, or HL+S performed for GSV insufficiency, and were followed up for five years. In the RFA group, the recurrence rate was the lowest, and the GSV occlusion rate was equal to the EVLA and HL+S groups but significantly better than in the UGFS group (Lawaetz et al. 2017a). In a review from 2015, the RFA closure rates were observed to be in the range of 88%–100% at 1–2 years (Goodyear and Nyamekye 2015).

When treating the GSV with thermal ablation, the AASV is usually left untreated and can cause recurrence down the line. The reason for AASV reflux after thermal ablation of the GSV can be either that it was missed in the initial preoperative ultrasound examination, or it is a true neoreflux; it has also been postulated that a heavy reflux into the GSV in the initial scan can conceal smaller reflux into the AASV (Anwar et al. 2019). It has been suggested that if the AASV has a direct confluence into the SFJ, its simultaneous treatment might be beneficial in order to prevent recurrence (Baccellieri et al. 2020). In a meta-analysis of RCT's with at least two years of follow-up, recurrence originating from AASV reflux was observed in 2.9% of patients after RFA (O'Donnell et al. 2016).

Different RFA catheters are provided by several manufacturers. The most common, and the one with the most profound evidence, is the Venefit procedure that utilizes the ClosureFAST catheter (VNUS Medical Technologies). The RFITT (Olympus Surgical Technologies Europe), EVFR (F Care Systems) and VeinCLEAR (RF Medical) devices are also used. In a recently published study, Venefit, RFITT and EVFR were compared to each other in terms of GSV occlusion in a randomized setting. The EVFR was found to produce a significantly lower occlusion rate at six months than RFITT and Venefit, but the quality of life was similar in all groups at 12 months (Nyamekye et al. 2019).

In a recent cost-effectiveness analysis spanning 5 years, RFA was found to have the highest median ranking for net benefit compared to HL+S, UGFS and other ablation methods (Epstein et al. 2018).

2.5 Endovenous laser ablation

2.5.1 Endovenous laser ablation: history and overview

Endovenous laser ablation (EVLA) uses laser light energy to cause thermal vein wall injury and the subsequent closure of the vein. In respect to endovenous thermal ablation methods, RFA came first, but EVLA followed soon after (Carradice 2014). The first to report the use of EVLA in varicose vein surgery was Dr. Carlos Boné (Boné 1999). With the first devices, the RFA procedure was slower, and its initial, somewhat inferior occlusion rates led to EVLA soon becoming the more popular of the two (Carradice 2014). The first wavelength fibre to be used in EVLA was an 810 nm diode laser with bare tip fibre (Min et al. 2001). Thereafter, higher wavelengths and radial fibres have been developed (Yamamoto and Sakata 2014).

In the EVLA procedure, the fibre is introduced into the vein via an introducer with the Seldinger technique, though for a slimmer fibre, a needle or cannula is sufficient. The tip of the fibre is usually placed 1–2 centimetres below the SFJ. The tumescent solution is then applied around the GSV, compressing it against the fibre and providing dissection from adjacent tissues. Thereafter, the laser generator is activated, and the fibre is pulled back continuously with controlled speed (Vuylsteke et al. 2019). The laser causes transmural thermal injury consisting of collagen denaturation, tissue desiccation, vaporization, and carbonization in the vein wall. This leads to fibrotic vein closure (Fan and Rox-Anderson 2008). The exact mechanism of energy delivery to the target tissue has been under debate, but the heat generated by the laser tip is probably the most important factor, with irreversible injury occurring when tissue is heated to 75 °C for at least one second (W. S. Malskat et al. 2014). Similar to RFA, many venous segments can be treated in one sitting.

2.5.2 Endovenous laser ablation: complications

Since both RFA and EVLA use thermal energy and are applied in a similar manner, the possible complications are also similar, including EHIT, DVT, PE, nerve injury, skin burns and ecchymosis (*Table 2* on page 66). According to a meta-analysis including 52 studies, the incidences of EHIT, DVT and PE after EVLA are similar to those after RFA: DVT 0.3% (95% confidence interval 0.2-0.5%) and PE 0.1% (95% ci 0.1-0.2%) (Healy et al. 2018). The saphenous nerve injury rate after EVLA is low: as reported in a meta-analysis, some 3.8% (95% confidence interval 2.4-4.5%) of patients reported paraesthesia. In approximately half of the cases, the paraesthesia

persisted at two years. Thermal skin injury is rare, at 0.31%; the frequency is equal with RFA and EVLA (Dermody et al. 2013). In another meta-analysis, the ratio of paraesthesia after EVLA was 6.73% (Pan et al. 2014).

2.5.3 Endovenous laser ablation: results

In 2001, Navarro et al published a series of 33 patients (40 GSVs) treated with EVLA. In a mean follow-up time of 4.2 months, all the treated GSV segments remained occluded and no major complications occurred (Navarro et al. 2001). Min et al reported on 84 patients (90 GSVs) receiving EVLA, with the 97% occlusion rate at one week persisting at 9 months. One case of paraesthesia was reported, but no other complications occurred (Min et al. 2001). At two years, the recurrence rate was lower than 7% (Min et al. 2003). Since these preliminary reports, the popularity of EVLA increased quickly. Perkowski et al. published a series of 165 patients (203 limbs) treated with EVLA in 2004, achieving a success rate of 97% (Perkowski et al. 2004). Disselhoff et al. reported the two-year follow-up of 85 patients (93 limbs) treated with EVLA, observing no recanalizations or recurrent GSV reflux (Disselhoff et al. 2005). A large single-centre series of patients treated with either EVLA or RFA reported no cases of recanalization of the GSVs at three years (Ravi et al. 2006).

An interesting early study compared EVLA to HL+S in the same patient (bilateral operation: EVLA in one leg and HL+S in the other), showing less bruising and swelling in the leg treated with EVLA; the patients favoured EVLA over HL+S (de Medeiros and Luccas 2005). The first RCT comparing EVLA to HL+S in two patient groups was published in 2007, declaring similar success rates for both groups at six months (L. H. Rasmussen et al. 2007). The two-year results revealed no recanalization in the EVLA group, and the recurrence rate for varicose veins was similar between the EVLA and HL+S groups (L. H. Rasmussen et al. 2010). An RCT comparing EVLA to cryostripping of the GSV showed a 95-percent GSV occlusion rate in the EVLA group at six months, with no recanalization detected at two years; neovascularization was observed in some of the patients in the HL+S group, but in none in the EVLA group. However, anterior accessory saphenous vein (AASV) reflux was observed in 10% of the patients in the EVLA group (Disselhoff et al. 2008).

In the 2010s, long-term (five years or longer) follow-up data from RCTs comparing EVLA with open surgery became available. Disselhoff et al. reported freedom from superficial venous incompetence at 5 years in 62% of patients after EVLA and in 51% of patients after surgery; this difference was not statistically significant (Disselhoff et al. 2011a). Rasmussen et al. published the five-year results of EVLA vs. HL+S in 2013, reporting no difference between the treatment groups in either recurrence or quality of life (L. Rasmussen et al. 2013). In the five-year results of the RELACS study comparing EVLA with HL+S, the overall clinical recurrence rate was similar between the two groups (Rass et al. 2015).

The pattern of recurrence seems to differ between thermal ablation and surgery, as discussed previously regarding RFA. Rass found that, in the EVLA group, reflux originating at the SFJ – most commonly in the AASV – was observed more frequently, while the recurrence in the surgery group mostly originated from perforators and the saphenopopliteal junction (Rass et al. 2015). Given that the SFJ remains open after thermal ablation, some studies were conducted to observe whether concomitant high ligation would result in a smaller recurrence rate. The five-year results of one such study showed that EVLA combined with HL did not prevent recurrence but, instead, resulted in more neovascularization (33% in contrast to 0% with EVLA only) (Disselhoff et al. 2011b). Flessenkämper et al. compared three groups – EVLA, EVLA combined with HL and HL+S – and found similarly that, at six years, the recurrence rate did not differ between the groups, whereas the distribution did. Reflux originating from the side branches of the GSV was more common in the EVLA group than in the other groups (Flessenkämper et al. 2016a). In a study comparing EVLA with HL+S, neovascularization in the groin was seen in 27.7% of HL+S patients and in none in the EVLA group at five years. In comparison, AASV recurrence was more common in the EVLA group. It was concluded that EVLA reduced the incidence of recurrence more effectively than surgery (Wallace et al. 2018a). In a meta-analysis, recurrence caused by AASV reflux was observed in 1.7% of patients after EVLA (O'Donnell et al. 2016).

EVLA has also been compared to UGFS and open surgery in a few studies with five-year follow-up. Van der Velden et al. found that EVLA and conventional surgery yielded superior occlusion rates compared to UGFS, and Brittenden et al. showed that EVLA lead to a better quality of life (Brittenden et al. 2019, van der Velden et al. 2015a). Lawaetz et al. likewise reported that EVLA, HL+S, and RFA all resulted in greater technical success compared to UGFS (Lawaetz et al. 2017a).

Since both EVLA and RFA aim to thermally injure the treated vein in order to produce long-term occlusion, it is interesting to compare the results of these two methods. In many studies, RFA is proposed to result in lower pain scores and less bruising in the immediate postoperative period. In a double-blinded study comparing EVLA and RFA, the pain scores and bruising were significantly lower in the RFA group, with similar occlusion rates at three months (Nordon et al. 2011). Nonetheless, according to a meta-analysis, RFA and EVLA were statistically equal in safety, pain scores after the treatment, and occlusion rates at one year (He et al. 2017).

The laser fibres used in EVLA have evolved, and several studies have compared different wavelengths and fibre types. Lower wavelengths specifically target haemoglobin, while higher wavelengths target water; since blood mainly consists of water, the significance of the wavelength has been under debate. Hirokawa et al. compared a bare-tip fibre to a 1,470-nm radial fibre in both a retrospective and a randomized prospective study, finding that the radial fibre produced fewer adverse effects, such as bruising and pain (Hirokawa and Kurihara 2014, Hirokawa et al.

2015). In another study with a follow-up of 48 months, a 980-nm laser fibre was compared with a 1,470-nm radial fibre. Paraesthesia, induration and ecchymosis was less frequent in patients treated with the 1,470-nm fibre, and the recanalization rate was lower (Arslan et al. 2017). It seems, though, that the wavelength should not be excessively high, as a 1,920-nm laser was found to produce inferior occlusion rates compared to the 1,470-nm laser (Mendes-Pinto et al. 2016). In a recently published meta-analysis, the long and short wavelengths produced similar occlusion rates, and the amount of energy administered (over or under 50 Joules per centimetre) did not affect the occlusion rates, although it was accepted that patient-measured outcomes such as pain scores might favour longer wavelengths (Malskat et al. 2019). New fibre tip modifications, such as the tulip fibre that aim to reduce the risk of perforating the vein wall have been developed and proved safe and effective (Bozkurt et al. 2019).

The Clinical Practice Guidelines of the ESVS on the Management of Chronic Venous Disease recommends endothermal ablation methods for GSV reflux in preference to both surgery and UGFS (Wittens et al. 2015).

2.6 Endovenous steam ablation

2.6.1 Endovenous steam ablation: history and overview

Endovenous thermal ablation can cause thermal injury to adjacent tissues, and especially EVLA creates high temperatures that can cause perforations of the treated vein wall, inducing perivenous inflammation. It has been hypothesized that steam could heat the vein homogeneously, thus avoiding perforations (Milleret et al. 2013). In endovenous steam ablation (EVSA), sterile water is heated and transformed into steam. Micro-impulses of the steam generated by the device (Steam Vein Sclerosis™, cermaVEIN, Archamps, France) are transferred into the vein lumen through a catheter (Mlosek et al. 2014).

The EVSA procedure is very similar to other endovenous thermal ablation methods. In EVSA, the steam delivery catheter is placed 3 cm below the SFJ, and steam impulses are applied at 1 cm intervals during catheter withdrawal. The linear endovascular energy density of a single steam impulse is 60 J according to the manufacturer; the number of impulses is adjusted on the basis of the diameter of the treated vein, with small veins receiving fewer and larger veins more impulses per centimetre (Mlosek et al. 2014). The heat of the steam produces vein wall necrosis, comparable to that caused by EVLA or RFA (Thomis et al. 2013). Tumescence anaesthesia is necessary; in practice, a larger volume of tumescent solution than in RFA or EVLA is needed to prevent the sensation of heat and pain due to the high-speed steam jet (Proebstle and van den Bos 2017). EVSA has failed

to achieve popularity, chiefly because it ultimately offers no real advantage over thermal ablation methods (Whiteley 2015).

2.6.2 Endovenous steam ablation: complications

As EVSA is a thermal ablation method, the possible complications are analogous to those caused by RFA and EVLA. The literature is scarce on this subject. In a prospective series of 64 patients treated with EVSA, there was one incident of a skin burn at the entry site, and one case of thrombus extension into the femoral vein was observed, but no DVTs occurred (Milleret et al. 2013). In a randomized study in which 117 patients were treated with EVSA, the incidence of complications was similar to EVLA, with the most common adverse event being thrombophlebitis (van den Bos et al. 2014).

2.6.3 Endovenous steam ablation: results

Data on the efficacy of EVSA is limited. In a small prospective study, 20 patients (25 GSVs in total) were treated with EVSA. Vessel occlusion was achieved in all cases, with the lumen of the vein decreasing during follow-up. One patient showed partial recanalization of the treated GSV at six months; the other treated veins remained occluded (Mlosek et al. 2014). Van den Bos et al. compared EVSA to EVLA in a randomized setting. Initially, the patients treated with EVSA received 1–2 pulses of steam per centimetre, but the amount was increased to at least 2/cm after the results of an experimental study showed that 2 pulses/cm are necessary to generate the desired effect. The patients receiving low-dose EVSA had a lower occlusion rate at one year than those in the EVLA group (96%), but in the high-dose EVSA group, the occlusion rate was 92% (van den Bos et al. 2014).

2.7 Mechanochemical ablation

2.7.1 Mechanochemical ablation: history and overview

Thermal ablation has obvious drawbacks. It involves the risk of damage to adjacent tissues, potentially causing nerve injury and skin burns, and can predispose to thromboembolism through EHIT. Thermal ablation necessitates the application of tumescent anaesthesia, causing discomfort to the patient and lengthening the operation. While UGFS has none of these disadvantages, its results are poor. Non-thermal ablation (NTA) methods are currently developed, aiming to be both minimally invasive and efficient. Mechanochemical ablation (MOCA) is one of these methods. In MOCA, a special infusion catheter system (ClariVein; Vascular Insights, Madison, CT, USA) containing a rotating dispersion wire is introduced into the vein. Local anaesthesia is only needed for inserting the sheath. Occlusion of the vein is

achieved through the simultaneous mechanical damaging of the epithelial wall and the dispersion of the injected sclerosant (either polidocanol or STS). In the procedure, the catheter is placed 1–2 cm below the SFJ and the catheter motor is then turned on, after which the infusion of the sclerosant is started. With the dispersion wire rotating at 3,500 rounds per minute (the speed can be adjusted between 2,000 and 3,500 rpm, but 3,500 is the default setting) and the sclerosant infusion ongoing, the catheter is slowly pulled back (Elias and Raines 2012, Mueller and Raines 2013). The amount of sclerosant used in the procedure is calculated based on the diameter and length of the treated vein, and the operator is responsible for infusing the sclerosant evenly while also maintaining constant pull-back with the correct speed at about 1.5 mm per second (Elias et al. 2013). The maximum dose of sclerosant is 10 ml per session; this limits the number of veins that can be treated at one sitting and the use of concomitant UGFS for tributary varicosities.

2.7.2 Mechanochemical ablation: complications

Most published studies on MOCA have excluded patients with a previous DVT or PE; previous thromboembolic complications are viewed as a contraindication for sclerotherapy. The data published so far yields NTA methods (MOCA and cyanoacrylate embolization) a combined risk ratio of 0.45 for DVT compared to thermal ablation. The risk of paraesthesia and skin pigmentation is significantly lower for NTA methods than for thermal ablation (Hassanin et al. 2019). The complications of MOCA compared to other treatment methods are compared in *Table 2* (page 66).

One striking case report of an inadvertent stripping of the treated vein has been published. The tip of the dispersion wire got stuck in a calcified side branch and, consequently, the whole vein was inversion-stripped. The patient, however, did not suffer any harm from this during a six-month follow-up period (Lane et al. 2015). Indeed, the tip of the device tends to stick to the valves, which is important to be aware of during the procedure.

2.7.3 Mechanochemical ablation: results

Initial safety and efficacy studies were published in 2011–2012. The immediate occlusion rate was reported to be 100%, but van Eekeren et al. found the six-week occlusion rate to be 87%, with most of the recanalizations partial (van Eekeren et al. 2011). Elias et al. observed a 96.7% occlusion rate at a mean follow-up of 260 days (Elias and Raines 2012). Van Eekeren et al. used polidocanol and Elias et al. STS. It has been discussed whether the use of different sclerosants accounts for the variation in the occlusion rates; STS is considered more potent (Mueller and Raines 2013).

The volume of sclerosant is a limiting factor in the use of MOCA. The maximum dose of polidocanol – in some countries the only sclerosant registered for use – is 2 mg per kilogram of body weight per day, and the accepted maximum volume of STS is 10 ml per patient. If the patient has bilateral large GSVs, they probably cannot be treated in one session. Concomitant UGFS for varicose tributaries is also limited by the maximum volume of the sclerosant, resulting in either not treating them at all, or the need for another treatment session. It has been postulated that microfoam could be used instead of a liquid sclerosant, thus overcoming the volume limit. Therefore, a study comparing MOCA performed with either 2% or 3% liquid polidocanol to 1% polidocanol microfoam was launched, but the study was soon discontinued, since it was found that, at six weeks, the occlusion rate with microfoam was only 30.4% compared as opposed to the respective 88% and 85.7% in the two liquid polidocanol groups (Lam et al. 2016).

In 2017, a meta-analysis including all ten of the available studies (none of which were RCTs) on MOCA was published. It was reported that the mean anatomical success rate was 92% at six months, 91% at one and two years and 87% at three years; however, there were only a few studies with a follow-up longer than six months (Witte et al. 2017). Another meta-analysis, also from 2017, concluded that the pooled anatomical success for MOCA was 94.1% at one year (Vos et al. 2017). In a newly published meta-analysis including all comparative studies on NTA techniques vs thermal ablation that were available before January 2019, NTA techniques were observed to be equal to thermal ablation in terms of the quality of life, VCSS and technical success at the study end point (Hassanin et al. 2019).

Only a few randomized studies on MOCA have been published. Lane and colleagues compared MOCA to RFA in a randomized setting, discovering that the pain scores during ablation were significantly lower in the MOCA group. At six months, the occlusion rates were 87% in the MOCA group and 93% in the RFA group; the difference was not statistically significant (Lane et al. 2017). The two-year results of the MARADONA trial (multicentre randomized controlled trial comparing mechanochemical endovenous ablation to radiofrequency ablation in the treatment of primary great saphenous vein incompetence) were recently reported: the 2-year occlusion rates were 80.0% in the MOCA group and 88.3% in the RFA group, but clinical improvement was similar in both groups. In the MOCA group, there were more cases of hyperpigmentation and more anatomic failures, consisting mostly of partial recanalization of the GSV (Holewijn et al. 2019).

An interesting retrospective study on patients with venous ulcers compared MOCA with thermal ablation in terms of ulcer healing, finding that MOCA yielded shorter healing times and a better ulcer healing rate. However, the patients treated with MOCA had more vein segments treated, and the sample size was relatively small (S. Y. Kim et al. 2019).

The cost-effectiveness of MOCA seems to be, on average, similar to EVLA, RFA and HL+S, although RFA had a slight advantage in the analysis (Epstein et al. 2018).

2.8 Cyanoacrylate embolization

2.8.1 Cyanoacrylate embolization: history and overview

Cyanoacrylates have been used as tissue adhesives and vascular closure agents in, for example, vascular malformations, intracranial aneurysms and in other occluding procedures, such as bile duct ablation. In contact with blood, cyanoacrylate (CA) forms an adhesive bond (Lawson et al. 2013). CA solidifies quickly, causing an inflammatory foreign-body reaction in the vein wall (Almeida et al. 2013). After promising animal model studies, a system for the cyanoacrylate embolization (CAE) of insufficient superficial veins was produced in the early 2010s. CAE is an NTA method, with no need for tumescence anaesthesia. The first report of use in humans with great saphenous vein insufficiency was published in 2012 (Almeida et al. 2013).

In CAE, a special delivery system (VenaSeal [Medtronic, USA], VariClose® Vein Sealing System [Biolas, Ankara, Turkey], Venablock™ or Veinoff™ [Invamed, Ankara, Turkey]) is inserted into the treated vein through a vascular sheath. The technique of the embolization depends on the system used. The VenaSeal is based on segmental ablation: the delivery catheter is first placed 5 centimetres below the SFJ, and two doses (0.1 ml) of glue 1 cm apart are administered. The device is then pulled back for 3 cm and the vein compressed for three minutes. Thereafter, further doses are applied 3 cm apart, with 30 seconds of compression over each one (Lawson et al. 2013). The VariClose delivery catheter is placed 3 cm below the SFJ, the SFJ is compressed, and the catheter is pulled back continuously at 2 cm per second, with the trigger for glue delivery pressed every 5 seconds or 10 centimetres to administer CA at 0.03 cc/cm. Finally, the whole treated vein segment is compressed for 30 seconds (Yasim et al. 2017). In the VenaBlock system, the delivery catheter is withdrawn at a slow steady rate, with continuous infusion of the glue (Parsi et al. 2019). Compression stockings need not to be used after CAE, and the patient can return to work the next day (*Table 2*, page 66).

No data on the safe maximum dose of CA exist; there is a consensus of an upper limit of 10 ml of adhesive per session, allowing a maximum of two long venous segments to be treated in one sitting (Parsi et al. 2019).

The CA glues used by the different manufacturers are somewhat different to each other. The VenaSeal uses a high-viscosity CA, designed to prevent embolization of the deep venous system. The VariClose glue has a lower viscosity, but a faster

polymerization rate. Currently, there are no studies that compare the different types of CA to each other (Radak et al. 2019).

It has been shown that the glue cast remains in the vein for at least three years after CAE, with a very slow breakdown. In a comparative study, the vein diameter decreased slowly during the three-year follow-up, but the vein, along with the glue cast, continued to be detectable; in patients treated with EVLA, over 80% had no visible vein left at three years (McGuinness et al. 2019).

There is yet no data available on whether the concomitant UGFS treatment of side branch varicosities is safe with CAE (Gibson et al. 2019). Phlebectomies can be performed simultaneously, but they require the use of local anaesthesia, essentially thwarting the idea of a non-tumescent treatment.

2.8.2 Cyanoacrylate embolization: complications

CAE has not been in use for long, but in the reports published so far, no DVTs have been described (Radak et al. 2019). The risk ratio of paraesthesia is, according to a late meta-analysis, 0.31 for NTA (including both CAE and MOCA) and 0.45 for DVT, when compared to thermal ablation (Hassanin et al. 2019). Extension of the glue into the SFJ has been reported (Parsi and Roberts et al. 2019). The complication rate of CAE compared to other treatment methods is presented in *Table 2* (page 48).

One specific condition that has been associated with CAE is phlebitis – the reddening of the skin and tenderness upon palpation; it has been reported in as many as over 20% of the patients. The reason for phlebitis remains unknown (Radak et al. 2019). Koramaz et al. used the VariClose system in their retrospective, comparative study and reported a phlebitis rate of only 2.1%, which was less than in patients treated with EVLA (7.9%). The patients recovered from phlebitis in an average of four days. The authors postulated that the low rate of phlebitis might be due to the low-viscosity CA used and its continuous application without pulsations (Koramaz et al. 2017).

CA can cause a type-IV hypersensitivity reaction that is not antibody-mediated and occurs 1–2 weeks after the first exposure. Mild reactions have been treated with both topical and oral steroids as well as antihistamines. In a case report, a patient with no previous allergy to glues developed persisting symptoms after CAE, with no adequate response to medication. The patient opted for a complete excision of the treated GSV to alleviate the symptoms. When patch-tested, she showed a moderate allergic reaction to CA (A. D. Jones et al. 2019). Another case report describing a serious reaction has been published; in this case, the vein was ultimately not excised (Nasser et al. 2019). In a prospective series from Korea, a phlebitis-like abnormal reaction (PLAR) was described in 25.4% of the patients treated with CAE, and in cases of bilateral operations, the condition was also

bilateral. The authors hypothesized that PLAR is a type-IV hypersensitive reaction and not merely local irritation. Interestingly, they also described that a suprafascial GSV is more common in an Asian population and that PLAR occurs more commonly in the suprafascial portion of the GSV. The authors have since started to administer intravenous dexamethasone immediately before CAE and non-steroidal anti-inflammatory drugs and antihistamines for 14 days after the treatment in addition to topical steroids in the case of itching and irritation (Park et al. 2019). Strikingly, both in this patient series and the two case reports, the VenaSeal system was used.

In histological biopsies, cyanoacrylate glue has been observed to cause lymphoid hyperplasia and extravenous foreign-body granulomas containing extruded glue. Previously, CA used as an embolic agent in different organ systems, such as the stomach, has been known to cause ulceration, abscesses and fistulae (Parsi et al. 2019). One case report of such a complication after treatment with VenaSeal has been presented: four months after bilateral treatment of the GSVs, the patient developed spontaneous skin perforations with an extrusion of glue pieces and growing granulomas along the GSV in both legs. The reaction was not alleviated with steroids. DDUS demonstrated movement of the glue in the proximal GSV, and eventually the GSVs had to be excised (Zernovicky 2018).

2.8.3 Cyanoacrylate embolization: results

The first results of CAE were very promising, with an occlusion rate 92% at 12 months (Almeida et al. 2013). Twenty-nine of the 38 treated patients were later available for the 36-month follow-up, and no additional failures were reported (Almeida et al. 2017). In subsequent non-comparative studies, the closure rate has been from 90.3% to 100% with follow-up ranging from six months to three years (Radak et al. 2019).

Bozkurt et al. compared CAE (the VariClose system) to EVLA in a prospective, non-randomized trial, finding closure rates of 95.8% for CAE and 92.2% for EVLA at 12 months (Bozkurt and Yilmaz 2016). In a retrospective study from Turkey, CAE (VariClose) was also compared to EVLA, with 12-month occlusion rates of 98.6% for CAE and 97.3% in the EVLA group (Koramaz et al. 2017). Ovali et al. performed a retrospective comparison of CAE (VariClose) with RFA, observing complete occlusion rates of 99.5% in the CAE group and 96.6% in the RFA group; the only failures were in the form of partial recanalization (Ovali and Sevin 2019).

Only a few randomized studies that compare CAE to thermal ablation have been published. Morrison et al. examined CAE (VenaSeal) in comparison to RFA, and in the 36-month results, the occlusion rate was 94.4% for CAE and 91.9% for RFA. The Quality of life (as measured by the AVVQ) and clinical severity (measured by the VCSS) were similar for both groups (N. Morrison et al. 2019). In a randomized study comparing CAE (VariClose) to EVLA, the reported 12-month closure rates were 94.1% in the EVLA group and 96.6% in the CAE group (Calik et al. 2019).

Currently, there are no results of comparative studies between CAE and MOCA, although one randomized study is in the recruiting stage (Belramman et al. 2018).

COMPARISON OF GSV TREATMENT METHODS

	Open surgery	UGFS	RFA	EVLA	MOCA	CAE
DVT	0.83%-5.3%	0.57-1.8%	0.3%	0.3%	0.2%	0%
Nerve injury/paraesthesia	5-58%	0%	4-7.8%	3.3%	<0.1%	0-2%
Wound infection	1.7-2.3%	-	-	-	-	-
Phlebitis	3%	4.4%	4-5.5%	4.9-5.6%	2-13%	0.5-18%
Return to work, days	4.3-19.8	1-2.9	1.6-12.2	1.3-7		1.0

Table 2. Comparison of GSV treatment methods. For DVT, data from Healy 2018, Critchley 1997, van Rij 2004, Ahmed 2018, Bergan 2006, Kulkarni 2013, Myers and Jolley 2008, O'Donnell 2015, Witte 2017, Bissacco 2018. For nerve injury/paraesthesia, data from Holme 1996, Sam 2004, Morrison 2003, Wood 2005, Dermody 2013, Hirsch 2017, Witte 2017, Vos 2017. For wound infection, data from Pan 2014, Dermody 2013, Vos 2017. For phlebitis, data from Dermody 2013, Vos 2017, Jia 2007, He 2017. For return to work, data from Rautio 2002, Lurie 2003, Rasmussen 2007, Rasmussen 2011, Kaltei 2008, Darwood 2008, Subramonia 2010, Eroglu 2018

AIMS OF THE STUDY

The purpose of this study was to determine the safety and efficacy of endovenous ablation techniques in the treatment of great saphenous vein insufficiency, as compared first to the previous gold standard of treatment – open surgery – and, subsequently, to established endothermal techniques, by performing randomized controlled trials.

The specific aims were:

1. To compare UGFS and EVLA to open surgery (HL+S) in terms of the GSV occlusion rates and the disease-specific quality of life at one year after the treatment. (I)
2. To study the long-term results of UGFS and EVLA in comparison to open surgery, recording the GSV occlusion rate, the disease-specific quality of life and the need for additional treatment. (II)
3. To examine the patient experience, feasibility and technical results of MOCA compared to endovenous techniques in the short term. (III)
4. To investigate the mid-term results of MOCA in comparison to EVLA and RFA, reviewing both the occlusion rates and the disease-specific quality of life. (IV)

3. METHODS

3.1 Studies I and II

Patients referred to the vascular clinics of Helsinki University Hospital and Tampere University Hospital for varicose veins between November 2007 and May 2010 were screened for eligibility in this study. Those who met the inclusion criteria and were willing to participate were enrolled in this prospective randomized trial.

The inclusion criteria comprised unilateral symptomatic GSV reflux as verified by DDUS, a mean diameter of the GSV at the thigh 5–10 mm and an age of 20–70 years. Patients with peripheral arterial occlusive disease, lymphoedema, a BMI of over 40 kg/m², pregnancy, allergy to either sclerosants or lidocaine, several general illness or a malignancy, past DVT, or a known coagulation disorder were excluded.

The randomization to receive either open surgery, UGFS or EVLA was performed according to block randomization (1:1:1) using sealed envelopes.

3.1.1 Procedures

Open surgery consisting of high ligation and stripping was carried out in the day surgery unit. Most patients were operated under general anaesthesia. The GSV was stripped in a retrograde fashion; in most patients, to just below the knee. A tumescent solution consisting of Ringer acetate (450 ml) with 1% lidocaine cum epinephrine (50 ml) was applied into the stripping tunnel. Phlebectomies were performed through small incisions using an Oesch phlebectomy hook. The groin incision was sutured using subcuticular stitches; phlebectomy incisions were closed with surgical tape. The leg was bandaged and covered in a support stocking. The patients were instructed to not remove the stocking and bandages before 48 hours after the procedure and, from there on, to use the stocking during daytime for up to two weeks postoperatively. A prescription for ibuprofen and paracetamol with or without codeine was provided.

The EVLA procedure was also performed in the day surgery unit. The patients received a light sedative (diazepam) before and during the procedure (alfentanil and/or propofol) if necessary. In the early phase of the study, a 980-nm diode laser fibre was used (Ceralas© D 980, Biolitec, Bonn, Germany), but it was replaced during the course of the study by the 1,470-nm radial fibre (ELVes©, Biolitec). The entry point of the fibre was, in most patients, just below the knee, and the tip of the fibre was placed at 1–2 cm below the SFJ. Tumescent anaesthesia was applied around the GSV under ultrasound guidance. A pulsed mode was used for the laser ablation with a 1.5 s impulse and 12 W power, aiming for administering energy at

70 Joules per cm. After ablation of the GSV, local phlebectomies were performed in a manner identical to the open surgery group, with similar aftercare.

UGFS treatment was performed at the outpatient clinic. The GSV was cannulated under ultrasound guidance, usually both at the proximal thigh and below the knee. Foam consisting of polidocanol 1% (Aetoxysclerol©, Kreussler, Wiesbaden, Germany) or STS in a concentration of 1% or 3% (Fibroveil™, STD Pharmaceutical Products, Hereford, UK) mixed with air in a 1:2 ratio was used. The flow of the foam as well as the spas of the vein were followed with ultrasound. Afterwards, a support stocking was applied, with instructions to use it continuously for three days, and, thereafter, during daytime for eleven days. All patients attended an appointment at one month for a DDUS examination. If any reflux was observed, a second treatment was carried out and the patient was again followed up on one month later, until the whole GSV was confirmed to be occluded.

3.1.2 Assessments

At baseline, the patients completed the AVVQ and the preoperative size of the GSV measured with DDUS was recorded.

During the procedure and at one week after the operation, the experienced pain was recorded using the Visual Analogue Scale (VAS) on a scale of 0–10. The length of the sick leave and complications were noted.

At the one-year follow-up, the patients were examined clinically and with DDUS to observe the status of the treated GSV. The AVVQ was again used to evaluate changes in the disease-specific quality of life.

At five years, the patients treated at Helsinki University Hospital were invited to a follow-up visit consisting of both a clinical and a DDUS examination as well as an assessment of the disease-specific quality of life with the AVVQ. The state of the GSV was recorded as either occluded/absent; partially recanalized with at least 5 cm of compressible, patent GSV; or completely recanalized. The leg was also imaged for other refluxing veins such as the AASV, and any neovascularization was noted. Any repeat treatments performed during the follow-up period were also recorded.

At both follow-up visits, if the patient was symptomatic and had either a refluxing, recanalized GSV or a new refluxing segment, they were assigned for additional treatment.

3.2 Studies III-IV

During 2014–2015, all patients referred to the Helsinki University Hospital vascular clinic for the treatment of varicose veins were screened for GSV insufficiency. The

patients fulfilling the inclusion criteria were invited to participate in the study. The inclusion criteria were: clinical classification C2–C4, ultrasound-verified reflux in the GSV, mean diameter of the GSV at the thigh between 5 and 12 mm, and an age of 20–75 years. The exclusion criteria consisted of a BMI over 40 kg/m², peripheral arterial occlusive disease, lymphoedema, pregnancy, allergy to either the sclerosants or lidocaine, severe general illness or a malignancy, previous DVT, previous varicose vein interventions in the same leg, and coagulation disorders.

Randomization was carried out by the study nurse after the appointment, using block randomization with sealed envelopes. The patients were randomized to three groups, EVLA, RFA and MOCA, in the ratio of 1:1:2.

3.2.1 Procedures

The treatments took place at a day surgery unit by a vascular surgeon familiar with all three techniques and were performed under ultrasound guidance.

In EVLA, the ELVes© fibre was used in a fashion identical to the previous study. In RFA, a VNUS ClosureFAST™ (VNUS Medical Technologies, San Jose, California, USA) was used. The entry point was at roughly the level of the knee, and the tip of the catheter was placed 1–2 cm below the SFJ. Tumescence solution was applied. The most proximal segment of the GSV was ablated twice, and, thereafter, each segment received one cycle of thermal energy.

In MOCA, the GSV was again accessed at knee height and the ClariVein© catheter was introduced with the tip placed at 1–2 cm below the SFJ. Catheter wire rotation was first activated for a few seconds to induce a spasm, and the infusion of sodium tetradecyl sulphate (Sotradecol®; AngioDynamics, Queensbury, New York, USA) began with the simultaneous withdrawal of the catheter. After the first 10 cm was treated, it was examined for flow, and if flow was present, the treatment was repeated. Thereafter, the rest of the GSV was treated. The amount of sclerosant used depended on the diameter and length of the treated GSV as per the instructions for use.

In all groups, after the ablation of the GSV, stab wound phlebectomies were performed. All wounds were taped, and the leg was covered with a compression stocking. The patients were instructed to use the stocking continuously for 48 hours and then during daytime for up to two weeks postoperatively. Patients received a prescription for paracetamol, with or without codeine, or ibuprofen, to be taken as necessary.

3.2.2 Assessments

At baseline, the patients completed the AVVQ. The mean diameter of the GSV at the most proximal 20 cm and at the thigh were documented. Reflux was defined as a retrograde flow of blood with a duration of over 0.5 seconds. Partial recanalization was defined as a segment of at least 5 cm of patent, compressible vein.

During and after the procedure, the perceived pain was recorded using the VAS, and the amount of medication administered was noted as well. At one month, the first follow-up was commenced; the occlusion of the GSV, wound healing, haematomas, nerve injuries and pigmentation were documented. The patients' perception of the optimal duration of the sick leave was recorded, as was the amount of pain medication they had taken. Any emerged complications were noted.

At both the one- and three-year follow-up visits, the leg was screened with DDUS to observe the occlusion of the GSV and reflux in any other superficial veins. Nerve injuries, pigmentation and the clinical status using the VCSS were recorded, and the AVVQ was used to compare the disease-specific quality of life to the baseline.

3.3 Statistical analysis

Data were evaluated by means of intention-to-treat analysis, but missing data was excluded. Continuous variables were reported as mean (SD) and range; data with skewed distribution are shown as median (IQR, range). Numerical data was compared using the paired-samples t-test and repeated-measures test (Study I) or one-way independent ANOVA (Study II). For data with skewed distribution, the Kruskal–Wallis test was used for analysis. Categorical values were compared using the χ^2 or Fisher's exact test. The association between recanalization and GSV diameter was determined by binary logistic regression. Statistical analysis, including life-table analysis, was performed using SPSS® for Windows® versions 19.0–22.0 (IBM, Armonk, New York, USA). The statistical significance level was set at $\alpha < 0.05$.

4. RESULTS

4.1 Study I

In total, 233 patients out of the 598 screened fulfilled the inclusion criteria and were willing to participate in the study. Nineteen patients were excluded after randomization, in most cases because of meeting an exclusion criteria not previously recognized. Hence, 214 patients underwent treatment; 18 were treated in Tampere University Hospital and 96 in Helsinki University Hospital. The treatment groups were similar in age, sex ratio, BMI, GSV diameter, CEAP class and AVVQ (

Table 3). All the patients attended the one-month follow-up visit, and 96.3% were available for the one-year follow-up visit (Figure 2).

	Surgery (n = 65)	EVLA (n = 73)	UGFS (n = 76)
Age (years)	47.3(11.3) (27-75)	47.0(13.4) (20-73)	48.3(12.7) (23-74)
Sex ratio (F : M)	55:10	55:18	58:18
BMI (kg/m ²)	25.1(3.7) (19-37)	25.2(3.6) (19-35)	25.8(4.6) (20-42)
Diameter of GSV (mm)			
at SFJ	8.7(2.0) (5-14)	8.5(2.2) (5-15)	8.4(1.7) (5-13)
below groin	6.6(1.3) (4-11)	6.8(1.2) (4-10)	6.7(1.2) (4-10)
mean	6.2(1.1) (4-9)	6.3(1.1) (4-8)	6.7(1.1) (4-9)
Baseline CEAP class			
C2	33	27	26
C3	26	36	37
C4	6	10	13
Baseline AVVQ	30.2(6.3) (16-45)	32.4(6.7) (18-51)	31.7(7.6) (13-52)

Table 3. Demographics and preoperative measurements. Values given as mean(SD) (range). Modified from Venermo et al. 2016.

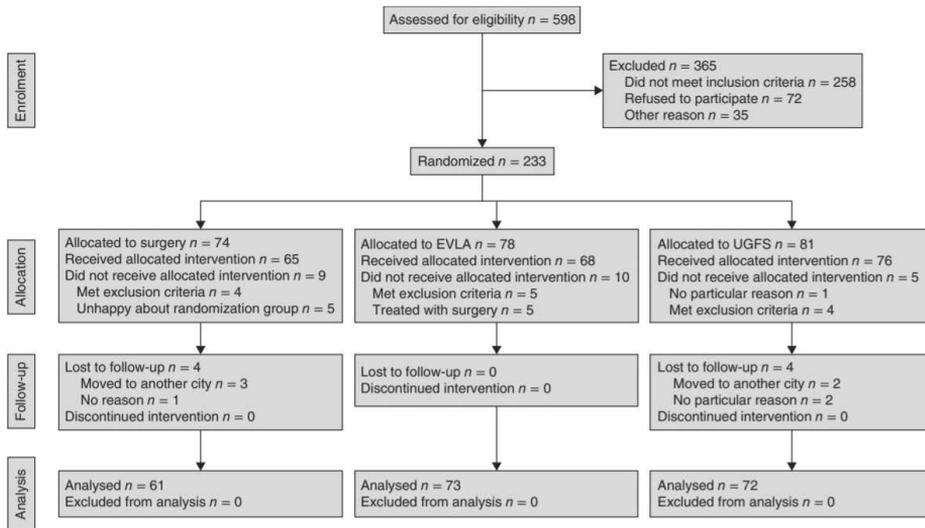


Figure 2. CONSORT diagram for Study I. Reprinted with permission from Venermo et al. 2016.

The whole procedure was faster in the EVLA group, with a mean duration of 83 minutes, compared to the open surgery group (mean duration of 95 minutes). The least painful – both at discharge and at one week after the treatment – of the three methods was UGFS, also being the one with the shortest prescribed sick leave (mean length 1 day, vs 8 days after EVLA and 12 days after open surgery). No major complications occurred. Three patients in the EVLA group and another three in the open surgery group developed a superficial wound infection requiring oral antibiotics.

At one year, the GSV was completely occluded or obliterated in 59 out of 61 (96.7%) patients after open surgery, in 71 out of 73 (97.3%) patients after EVLA and in 37 out of 72 (51.4%) after UGFS; the difference between the groups was significant ($P < 0.001$) (Figure 3). None of the patients in the open surgery group had a patent GSV in a DDUS examination, while two (3%) in the EVLA group did; these veins were small in diameter and asymptomatic. In comparison, 14 (19%) patients in the UGFS group had a patent GSV.

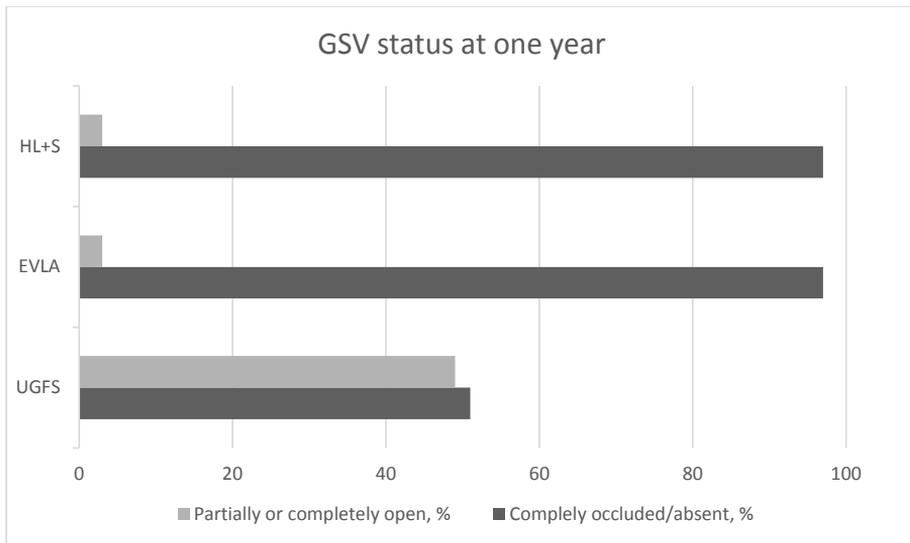


Figure 3. GSV status at one year. Data from Study I

The preoperative diameter and the patency of the GSV at one year were heavily correlated in the UGFS group: the larger the vein, the more likely it was to be either partially or completely recanalized (*Figure 4*). In the UGFS group, 11 patients (15%) were scheduled for a repeat treatment of the GSV: 2 to open surgery, 5 to EVLA and 4 to repeat UGFS. In the open surgery group, 4 patients (7%) were scheduled for additional treatment for tributary veins, while the same applied to one patient (1%) in the EVLA group.

The disease-specific quality of life as measured with the AVVQ improved in all groups from the baseline, with no differences between the groups at one year.

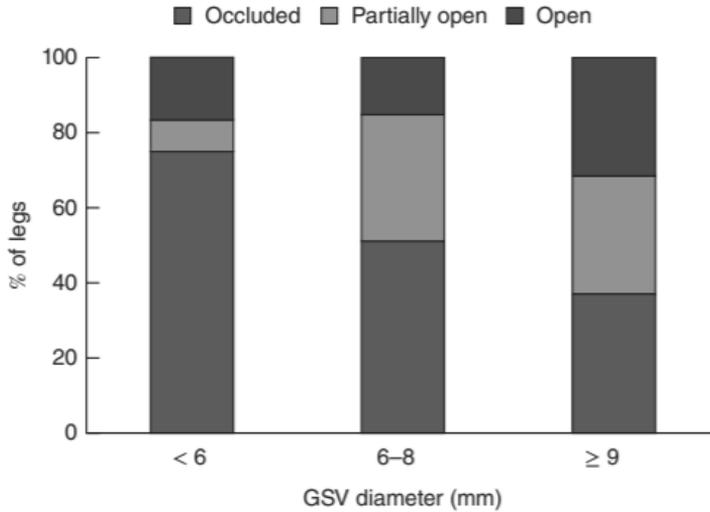


Figure 4. UGFS treated veins: preoperative diameter and occlusion at one year. Study I. Reprinted with permission from Venermo et al. 2016.

4.2 Study II

At five years, 166 (84.7%) of the 196 patients that were originally treated at Helsinki University Hospital attended the follow-up. The follow-up for the 18 patients treated at Tampere University Hospital could not be arranged. The GSV was completely occluded or absent in 48 of the 50 patients in the open surgery group (96.0%), in 51 of the 57 patients in the EVLA group (89.4%) and in 30 of the 59 patients in the UGFS group (50.8%) ($P < 0.001$). However, many patients in the UGFS group had already received a repeat treatment, and the unassisted (no additional treatment for varicosities on the same leg) occlusion rate in this group therefore was only 41.0% (16 out of 39 patients). In the open surgery and EVLA groups, the unassisted occlusion rates were 96.0% and 89.4%, respectively (Figure 5). The anatomical success rate (occlusion without further treatments of the GSV) produced by UGFS was 27.1% (16 out of 59).

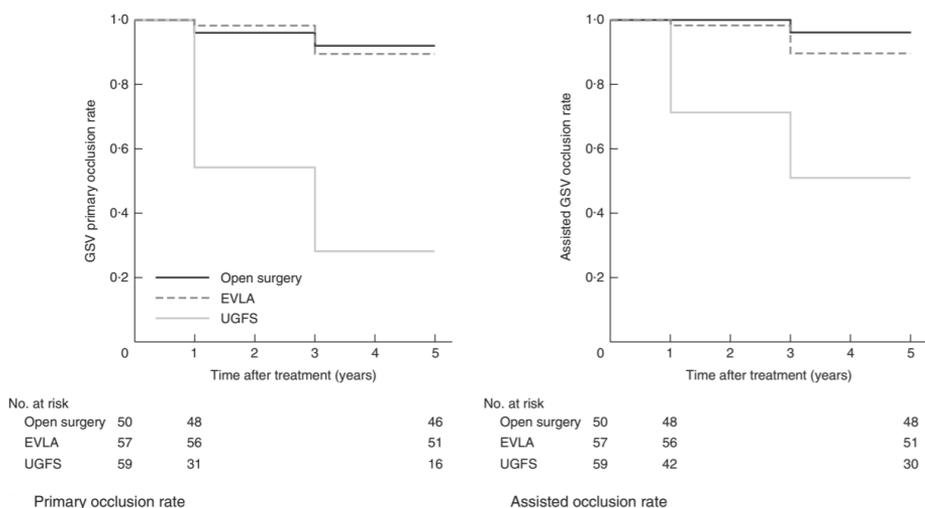


Figure 5. Primary and assisted occlusion rates of the GSV. Study II. Reprinted with permission from Vähäaho et al. 2018.

At five years, no correlation between the preoperative size of the GSV and the occlusion rate could be seen in any of the treatment groups.

The disease-specific quality of life at five years was not significantly different between the groups, with a mean AVVQ score of 8.7 in the open surgery group, 9.6 in the EVLA group and 11.2 in the UGFS group.

Many patients needed additional treatment during the follow-up period or were scheduled for such treatment at the follow-up visit. The odds of needing a repeat treatment were 8.5 times higher for the UGFS group than for the EVLA group; accordingly, the OR for the open surgery group was 1.6 times higher than for the EVLA group. The distribution of venous segments in need of supplementary treatment was different between the groups, with 25 patients in the UGFS group requiring a repeat treatment for the thigh GSV, as opposed to 2 in the open surgery group and 1 in the EVLA group. Four patients in the EVLA group and three in the UGFS group were treated for AASV reflux, but none for neovascularization; in comparison, two patients in the open surgery group needed treatment for neovascularization, but none for AASV reflux (*Table 4*).

	Open surgery (n = 50)	EVLA (n = 57)	UGFS (n = 59)
repeat treatment for GSV	2	1	25
AASV	0	4	3
neovascularized segments	2	0	0
under-the-knee GSV or tributaries	5	2	4
received additional treatment, total	9	7	32

Table 4. Additional treatment by venous segment in each study group. Study II. Modified from Vähäaho et al. 2018.

No major complications occurred in the study group during the follow-up. Skin pigmentation was still visible in 4% of the open surgery patients, in 2% of the EVLA patients and in 2% of the UGFS patients. One patient in each group had persisting paraesthesia.

4.3 Study III

One-hundred and thirty-two patients were randomized in this study; however, ultimately, 125 received the treatment (*Figure 6*). The treatment groups were similar in age, BMI, the initial size of the GSV, and the C classification (*Table 5*). All 125 patients attended the one-month follow-up, and 117 (93.6%) participated in the one-year follow-up.

	MOCA (n = 59)	EVLA (n = 34)	RFA (n = 32)
Age (years)	50.9(12.0)	49.5(11.9)	50.3(13.9)
BMI (kg/m ²)	26.1(4.2)	25.9(4.2)	26.3(4.8)
Mean diameter of thigh GSV (mm)	6.7(1.6)	6.5(1.6)	6.4(1.8)
C classification			
C2	32	20	18
C3	14	6	7
C4	13	7	7
missing	0	1	0
Side treated			
right leg	32	17	16
left leg	27	17	16

Table 5. Patient characteristics. Values are expressed as mean(SD). Modified from Vähäaho et al. 2018.

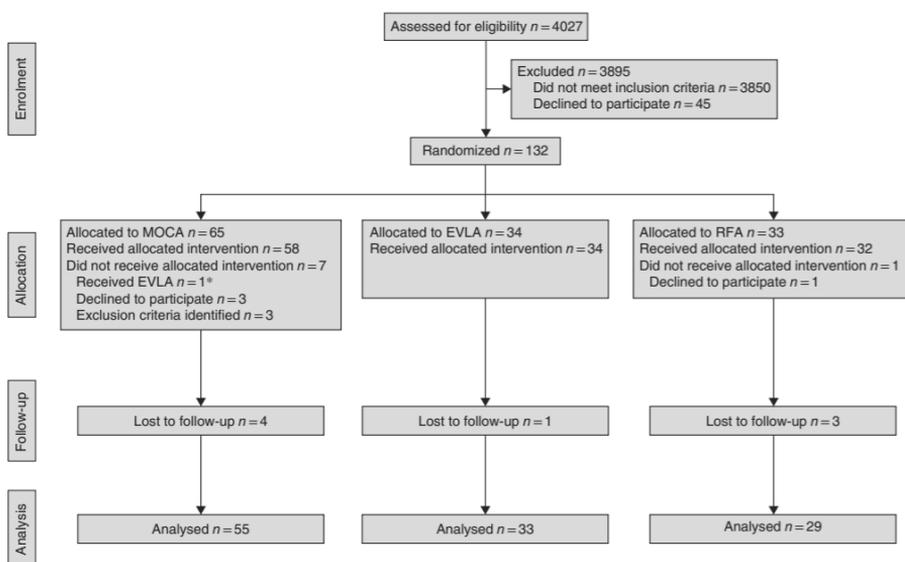


Figure 6. CONSORT diagram, Study III. * Cross-over to EVLA but analysed in the MOCA group. Reprinted with permission from Vähäaho et al. 2019.

During the follow-up, at one month, all the treated GSVs were occluded in the DDUS examination. At one year, the GSV was completely occluded in all patients in the EVLA and RFA groups. In the MOCA group, the occlusion rate was 81,8% (45 out of 55 patients). Among the ten patients with incomplete occlusion, there was one complete recanalization of the GSV and one patient with recanalized sections throughout the vein. The proximal GSV was recanalized but the thigh part occluded in five patients, and three patients had partial recanalization only in the thigh part of the GSV.

In the proximal GSV, there was a strong association between recanalization and the preoperative diameter of the GSV: when the diameter of the vein increased, the odds of it remaining occluded decreased (OR 0.31, 95% confidence interval 0.13–0.75). The mean GSV diameter before surgery was significantly larger in those with proximal recanalization at one year compared to those in whom the proximal GSV was completely occluded ($P = 0.007$) (Figure 7).

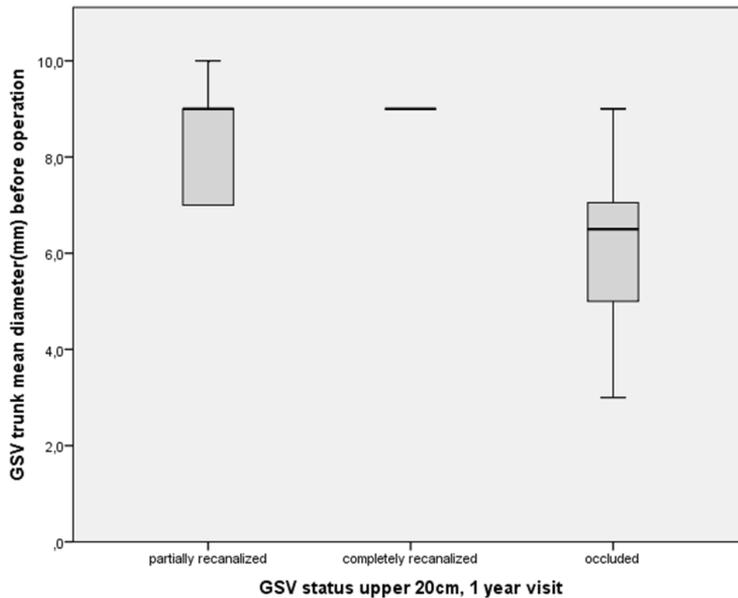


Figure 7. The preoperative size of the GSV and recanalization of the proximal GSV at one year. Data from Study III.

Those treated with MOCA received less propofol during the treatment; concerning other medications, there were no differences between the groups. Other measures assessing the treatment from the patients' perspective (pain during and after the treatment and at one week, the length of the sick leave, the amount painkillers taken at home) were statistically invariable between the groups.

No paraesthesia was evident at one year in the MOCA group, but three patients in the EVLA group and two in the RFA group reported paraesthesia; the affected area was smaller than 10 cm² in all cases.

The disease-specific quality of life, as measured with the AVVQ, improved from the baseline in all treatment groups. No differences arose between the groups at the baseline or at one year.

4.4 Study IV

One hundred and six patients (84.4%) attended the three-year follow-up. In the EVLA and RFA groups, the occlusion rate of the GSV remained at 100% (31 out of 31 patients in the EVLA group, and 25 out of 25 in the RFA group). In the MOCA group, the occlusion rate was 82.0% (41 out of 50 patients); the unassisted occlusion rate was, however, 80.0%, because one patient had received repeat treatment of the GSV with laser ablation.

The preoperative size of the proximal GSV predicted its occlusion at three years (OR 0.513, 95% c.i. 0.29–0.92), and, likewise, the diameter of the thigh part of the GSV correlated with its occlusion rate (OR odds ratio 0.465, 95% c.i. 0.25–0.87) (*Figure 8*).

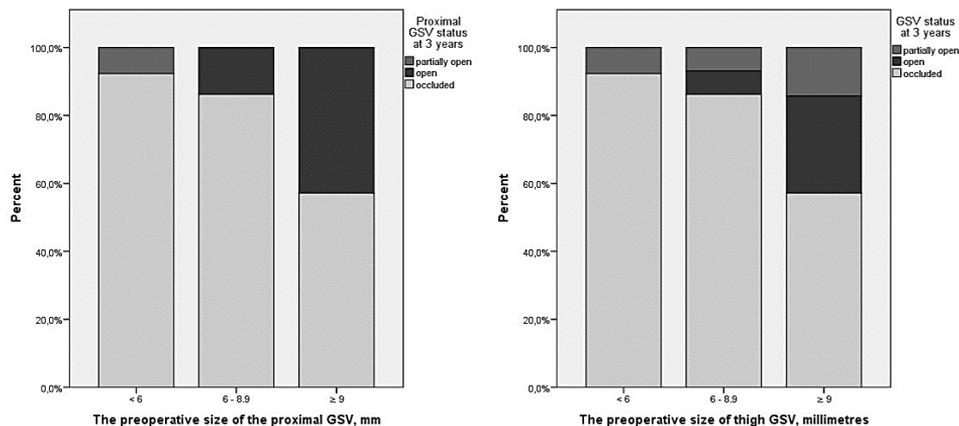


Figure 8. The preoperative size vs. occlusion at three years. Data from Study IV.

In most patients, the partially recanalized sections of the GSV progressed to more recanalization at three years (*table 6*).

One-year follow-up	Three-year follow-up
Partial recanalization of the proximal GSV with an occluded thigh GSV, 4 patients	<ul style="list-style-type: none"> • Complete recanalization of the whole GSV, 1 patient • Complete recanalization of the proximal GSV and partial recanalization of the thigh GSV, 2 patients • Occluded GSV after repeat treatment with EVLA, 1 patient
Recanalization of the proximal GSV with an occluded thigh GSV, 1 patient	<ul style="list-style-type: none"> • Recanalization of proximal GSV and partial recanalization of thigh GSV, 1 patient
Partial recanalization of the whole GSV, 1 patient	<ul style="list-style-type: none"> • Complete recanalization of the whole GSV, 1 patient
Partial recanalization of the thigh GSV with an occluded proximal GSV, 3 patients	<ul style="list-style-type: none"> • Complete recanalization of the whole GSV, 1 patient • Occlusion of the whole GSV, 1 patient • Lost to follow-up, 1 patient

Table 6. Partial recanalization at one and three years. Data from Study IV.

The average AVVQ scores at three years were 7.0 for the MOCA group, 6.2 for the EVLA group and 5.6 for the RFA group, with no significant differences between the groups.

The clinical status of the patients was recorded with the VCSS. The mean preoperative VCSS was 6.4 in the MOCA group, 6.2 in the EVLA group and 6.3 in the RFA group. The three-year mean values were 2.1, 1.7 and 2.1, respectively; all had improved from the baseline, and the groups did not differ from each other at baseline or at three years.

In the course of the follow-up period, one patient in the MOCA group received a repeat treatment of the GSV with laser ablation, and another underwent sclerotherapy for branch varicosities; two patients had been scheduled for laser ablation, and a few patients were waiting for consultation on possible additional treatment. None of the patients in either the EVLA or the RFA group had received additional treatment, but two in the RFA group were scheduled for the treatment of branch varicosities at the three-year follow-up.

Paraesthesia occurred in none of the patients in the MOCA group at three years; in contrast, two patients in the EVLA group and one in the RFA group reported persisting paraesthesia. The areas of sensory disturbances had, however, become smaller during the follow-up.

5 DISCUSSION

5.1 Limitations

The presented studies are all randomized, but neither the patient nor the operator was blinded to the type of treatment. The assessors were also aware of the treatment the patients had undergone at follow-up visits; in Studies I and II, the scarring would have revealed this in any case. The inclusion criteria for the studies were quite strict, and, as seen in the results of Study III, the majority of patients at the Helsinki University Hospital venous outpatient clinic did not meet the criteria: many had bilateral venous insufficiency or insufficiency in both the GSV and another trunk such as the SSV, and many had undergone previous treatments for varicose veins, not to mention the scrupulous exclusion of any concomitant diseases. Thus, the study populations do not represent the average patients seen for superficial venous insufficiency; the results, however, can be considered to give an accurate comparison of the efficacy of the treatment methods in GSV insufficiency. Not all patients were available for the longer-term follow-ups, but the follow-up percentages were still acceptable, with 84.7% of the patients in Study II and 84.4% in Study IV. For Studies III–IV, patient recruitment was slower than expected, and the recruitment was therefore stopped short of reaching the target of 160 patients. This reduces the power of these studies.

In all the studies, if the allocated intervention was other than UGFS, the patients underwent concomitant phlebectomies. Excising varicose segments of the GSV after thermal ablation of the trunk increases the occlusion rate, an advantage that UGFS does not obtain. From experience, it is known that for most patients, the most painful part of the procedure is when tumescent solution is applied around the superficial branch varicosities, and sometimes a repeat injection of local anaesthesia is necessary to complete the phlebectomies. Therefore, the pain scores recorded might not reflect the unpleasantness of the GSV ablation, but rather the pain caused by phlebectomies. There is an ongoing debate as to whether the treatment of branch varicosities should be performed concurrently or delayed. It is likewise unknown whether the best method of treating them is UGFS or phlebectomies, though an ongoing trial promises to shed light on this issue (Belramman et al. 2019). Most patients prefer a single-setting treatment over a delayed scheme, and if the phlebectomies are done concurrently to the ablation procedure, the quality of life and VCSS scores remain better for at least the first year (Lane et al. 2015). No conclusive data comparing the cost-effectiveness of these two approaches has been published. Hence, the ongoing practice of performing phlebectomies simultaneously with main trunk ablation can be justified.

5.2 UGFS (I, II)

UGFS has the advantage of being very minimally invasive, requiring only cannulation and no anaesthesia. The sick leave after UGFS is usually short, if needed at all. However, Studies I and II show that the occlusion rate for UGFS is significantly lower than for either open surgery or EVLA and that UGFS without repeat treatments produces a very modest occlusion rate of 27%. Also, patients treated with UGFS are 8.7 times more likely to require additional treatment than those treated with EVLA. At one year, the occlusion rate in the UGFS group correlated with the preoperative size of the GSV, with smaller veins being more likely to remain occluded. At five years, this correlation had vanished. The most likely reason for this is that at five years, the recanalized and symptomatic veins had already received repeat treatment.

In this study setup, the UGFS treatment was not standardized: the choice of sclerosant as well as the amount used was based on the experience of the vascular surgeon, much like in real life practice. This variation was at least partially overcome by following the patients up and repeating the treatment until the GSV was observed to be completely occluded in a DDUS examination. After this, though, the patients were not examined until the one-year follow-up; it can be argued that earlier repeat treatments might have resulted in a better occlusion rate – but also in more frequent visits to the clinic with limited resources. The foam used was made in a sclerosant-to-air ratio of 1:2, thus being more concentrated than in many other studies; however, the effect of this is unknown, as the optimal recipe for foam is yet to be determined. The choice of injection sites was left at the surgeon's discretion, even though this might affect the outcome, since the active concentration of sclerosant falls progressively from the injection site (Connor et al. 2014). Cavezzi and Tessari recommend that the first injection site should be 10-20 cm below the SFJ to maximise the effect of foam in the proximal GSV based on their own experience and a consensus conference (Cavezzi and Tessari 2009). The shortcomings of UGFS, one of which is the lack of standardization, have led to the development of catheter-directed foam sclerotherapy, enabling a more consistent treatment and possibly yielding better occlusion rates. However, this technique involves application of tumescent liquid around the vein (S. Y. Lim et al. 2020).

The disease-specific quality of life was statistically similar between all the treatment groups at both one and five years in Studies I–II. A tendency towards a greater AVVQ score in the UGFS group, indicating a lower quality of life, however, can be seen. The study may be underpowered for this difference to reach statistical significance, but it is in concert with other studies that have produced a clear difference in favour of open surgery and EVLA compared to UGFS (Brittenden et al. 2019, Kalodiki et al. 2012).

Our results, as well as the results of other randomized trials, discourage the use of UGFS for primary GSV insufficiency (Brittenden et al. 2019, Lawaetz et al. 2017a, van der Velden et al. 2015a). UGFS has its place in the treatment of branch varicosities and recanalized sections not suitable for endovenous ablation. Furthermore, it is the treatment of choice for telangiectasia and reticular veins. The ESVS guidelines suggest limiting the use of UGFS to veins with a diameter of under 5–7 mm (Wittens et al. 2015). The Finnish Current Care Guidelines state that if thermal ablation is not possible, a small venous trunk can be treated with UGFS (Current Care Guidelines 2016). If patients are treated with UGFS, they should be aware that the initial advantages of UGFS might be negated by the subsequent likely need of repeat treatment.

5.3 EVLA (I-IV)

At the beginning of recruitment for Study I, open surgery still prevailed in many venous clinics. Endovenous techniques were on their way, but long-term results were still awaited. The results of Studies I–II demonstrate the non-inferiority of EVLA compared to open surgery (HL+S). The rate of occlusion or obliteration was similar at one year, and the good occlusion rate obtained with EVLA was maintained through the five-year follow-up. Also, the procedure times were shorter in the EVLA group, and patients reported less pain and needed shorter sick leaves after EVLA. In Studies III and IV, EVLA was compared with MOCA and RFA, with both thermal ablation methods producing an excellent occlusion rate of 100% that was maintained through the follow-up period of three years.

It is interesting that EVLA and open surgery produce very different recurrence types. In EVLA, the SFJ is usually spared and left open as a conduit for proximal branches, such as the inferior epigastric vein. High ligation, in contrast, blocks the normal venous flow from superficial tissues of the lower abdomen and the pudendum, and it has been hypothesized that this might create venous hypertension, aggravating new venous growth or the enlargement of small veins (Pichot et al. 2000). This process leads to neovascularization, the all too familiar sight upon DDUS when examining a patient with previous HL+S: tortuous, thin-walled veins connecting the femoral vein with superficial veins. In our study, two patients treated with open surgery exhibited significant neovascularization that required treatment; however, the proportion can still increase, as neovascularization can emerge later, even over 10 years after the surgery (Winterborn et al. 2004).

After EVLA, most of the treated veins decrease in diameter and eventually leave behind only a small fibrotic scar. Subsequently, at three years, over 80% of the treated veins are no longer visible in DDUS (McGuinness et al. 2019). At this point, recanalization is not possible; any recurrence at the location of the GSV must be

neoreflux. In open surgery, even though the vein is removed completely, strip-tract neovascularization can occur, most likely as a response to the injury and haematoma caused by the stripping (Ostler et al. 2015).

In some 7% of the patients in the EVLA group in Studies I–II, reflux originating from the AASV was observed. AASV reflux can occur due to true neoreflux or be a missed reflux at the initial DDUS examination (Theivacumar et al. 2007, Rass et al. 2015, Anwar et al. 2019). The reflux into the AASV can be so mild in the initial scan that it is unnoticed, but it can become exaggerated after the GSV is ablated. Following thermal ablation of the GSV, neoreflux into para-axial veins is seen in 8%–31% of patients (Anwar et al. 2019). In a recently published study, it was proposed that if the AASV has a direct confluence into the SFJ instead of draining into the GSV, it should be treated simultaneously to avoid recurrence from it in the future (Baccellieri et al. 2020). Nonetheless, the AASV often has a straight proximal trunk under the superficial fascia and is therefore easily treated with endovenous techniques, should it become symptomatic. All in all, it seems that recurrence cannot be entirely prevented, whatever the treatment method; for reasons yet unknown, the superficial venous disease tends to progress as time passes, causing more veins to turn incompetent.

Thermal ablation has become the front-runner of treatment for superficial venous insufficiency. It has been successfully implemented in outpatient clinic use as well, saving operating room costs; this is something that open surgery would never be suitable for. However, EVLA and RFA, no matter how established, now face the challenge of competing against non-thermal ablation methods.

5.4 MOCA (III-IV)

Studies III and IV compare mechanochemical ablation with thermal ablation. MOCA yielded a one-year occlusion rate of 82% and an unassisted occlusion rate of 80% at three years. These are clearly inferior to the results of EVLA and RFA, both producing a 100% occlusion rate that was sustained for three years. Previous studies on MOCA have given slightly higher occlusion rates, though Holewijn and colleagues recently reported a mere 80% anatomic success rate at two years (P. S. Kim et al. 2017, Witte et al. 2017, Holewijn et al. 2019). Our results also indicate that larger veins treated with MOCA tend to recanalize more frequently. In this regard, MOCA resembles UGFS. Given the lower occlusion rates with MOCA, it could be reasonable to offer it as an alternative to thermal ablation if the patient is unwilling to tolerate the needle pricks necessary for the application of tumescent anaesthesia.

The disease-specific quality of life as measured with the AVVQ, as well as the clinical severity of the venous disease recorded with VCSS, were not statistically

different between treatment methods at three years. It has been suggested that the occlusion rate as an outcome is not that relevant; however, in Study II, a low occlusion rate lead to a manifold increase in additional treatments during the follow-up, a fact that cannot be disregarded.

In our study, the quite often observed proximal recanalization of the GSV in the MOCA group lead to recanalization “spreading” downwards during the follow-up period. The incompetence of the proximal GSV may cause venous pressures to rise caudally, explaining why the occlusion of the proximal GSV seems to be crucial in maintaining the occlusion of the more distal part of the vein. To combat proximal recanalization, the proximal part is treated twice in the MOCA procedure, if reflux is still present after the first run. In our study, however, this did not prevent recanalization.

The lower occlusion rate of MOCA could be overcome by using it only in smaller veins, perhaps with diameters of under 6–7 mm. MOCA has the advantage of not needing tumescent anaesthesia; this expedites the treatment and makes it optimal for outpatient setting. The nerve injury rate in this study was zero, as the method does not predispose tissues to thermal injury, which is another significant advantage. Since nerve injury needs not be feared, the below-the-knee GSV can also be safely treated, and in the case of a venous ulcer, the treatment can also be performed in a retrograde fashion, with the entry point at the proximal calf. This is a definite asset of MOCA. In contrast to thermal ablation, MOCA does not utilize a generator; therefore, the costs of setting up a practice using MOCA are lower, as the only thing needed along with the DDUS equipment is the single-use delivery catheter system.

MOCA, however, has some additional restrictions to its use. The amount of sclerosant per patient is limited to 10 ml by international consensus. If the patient has, for example, bilateral long GSVs with large diameters, they cannot be treated in one session. In addition, MOCA has some absolute contraindications, such as a PFO or an allergy to the sclerosant in use, as well as relative contraindications, such as a previous DVT.

The delivery catheter system used in MOCA is user-dependent, and the procedure has a learning curve; initially, when first learning the technique, the typical error is to pull the catheter back too fast and inject the sclerosant too slowly (Elias et al. 2013). The most popular type of RFA catheters employs a segmental ablation, leading to very standardized and repeatable results. In turn, EVLA depends on the continuous withdrawal of the fibre, but, presently, a machine has been developed for withdrawing the catheter at a constant rate, removing the possibility of erroneously pulling the fibre back too fast. The dispersion wire of the MOCA delivery catheter sometimes gets caught in vein valves or branches; this is first heard as the motor noise changes audibly, and then felt by either the operator or the patient. At this point, the motor and pull-back should be stopped, the wire re-

sheathed and tugged distally to free it, then advanced again proximally and un-sheathed, and the treatment resumed (Mueller and Raines 2013). This possibility of snagging on tissue unfortunately excludes the possibility of an automatic pull-back machine for MOCA. If at least the injection of the sclerosant could be somehow made automatic, the operator could concentrate on the withdrawal of the catheter, possibly leading to a more consistent ablation of the vein. Therefore, the design of the delivery catheter leaves room for improvement.

5.5 Future prospects

Endovenous thermal ablation is still the preferred method of treating superficial venous insufficiency (Bozkurt et al. 2019). The risk for complications is low, the excellent closure rates are maintained through years of follow-up, and no adverse long-term sequelae have emerged during more than 15 years of use. The fibres and catheters used in thermal ablation have evolved, leading to even better results. Thermal ablation can be performed in local anaesthesia, which even further diminishes the risk of complications, and in an outpatient setting with low costs. In essence, thermal ablation has replaced open surgery and displacing it in turn with other treatment methods will prove difficult.

NTA methods, however, are here to stay. Cyanoacrylate embolization in particular is gaining popularity: it is easy and quick to apply, and no compression stocking is needed afterwards. Nonetheless, the long-term efficacy of CAE is not yet established, and it leaves behind a foreign body of glue that can be allergenic or may dislodge from the vein – the effects of the glue column in the long run remain unknown.

A new contender is high-frequency ultrasound (HIFU). In HIFU, a focused transducer (Sonovein®, Theraclion, France) is used to cause localized hyperthermia (85°C) that produces the occlusion of the vein. The device also includes a single-use membrane and a liquid for cooling and coupling to protect against a thermal injury of the skin and adjacent tissues. HIFU is a completely noninvasive method: the treated vein does not need to be cannulated, and no sterile field nor anaesthesia is required. It is purportedly a good method for treating tortuous veins, such as groin neovascularization. Obermayer released the first report on venous HIFU in 2019: 50 legs with varicose veins were treated with HIFU and followed up for three months; the results were excellent at least in the terms of aesthetic improvement and elimination of pain (Obermayer 2019). Whiteley likewise reported in 2019 having treated five patients with HIFU (Whiteley 2019). However, as promising as HIFU sounds, the Sonovein system only just received its CE marking in the EU, and there is no data available so far on its safety and efficacy, not to mention the long-term results.

6. CONCLUSIONS

1. UGFS resulted in a significantly lower occlusion rate at one year compared to open surgery, while EVLA was noninferior to open surgery. The disease-specific quality of life was similar between the groups.
2. At five years, EVLA and open surgery resulted in similar occlusion rates, with patients treated with EVLA needing the least number of additional treatment. The occlusion rate in the UGFS group was inferior to both open surgery and EVLA, with the odds ratio for requiring additional treatment being 8.7 times greater than in the EVLA group. The differences in disease-specific quality of life between the groups were not significant, although a trend towards a lower quality of life in the UGFS group could be contemplated.
3. Patients treated with MOCA needed less medication during the treatment than those treated with either RFA or EVLA. None in the MOCA group were afflicted with nerve injury in comparison to three patients in the EVLA and two in the RFA group. However, the occlusion rate of the treated GSVs was lower after MOCA (82%) than after EVLA or RFA (100%).
4. The unassisted occlusion rate of the GSVs in the MOCA group was 80%, being significantly inferior to the maintained rate of 100% in the EVLA and RFA groups. Recanalization was mostly observed in veins larger than 6 mm in diameter. The proximal recanalizations observed in the MOCA group 12 months after the treatment progressed during the three-year follow-up. Clinical status, as measured with the VCSS, and disease-specific quality of life did not differ between the groups.

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REFERENCES

- Aber A, Poku E, Phillips P, Essat M, Buckley Woods H, Palfreyman S, Kaltenthaler E, Jones G and Michaels J. Systematic review of patient-reported outcome measures in patients with varicose veins. *Br.J.Surg.* 2017, 104:1424-1432
- Ahmed M S, Lutze S, Tembulatow M, Daeschlein G, Junger M and Arnold A. Long-term outcome of open surgery in CVI patients concerning postoperative complications, perioperative hemodynamics and clinical efficacy, Part I. *Clin.Hemorheol.Microcirc.* 2018, 70:399-411
- Ahti T M, Makivaara L A, Luukkaala T, Hakama M and Laurikka J O. Effect of family history on the risk of varicose veins is affected by differential misclassification. *J.Clin.Epidemiol.* 2010, 63:686-690
- Al Shakarchi J, Wall M, Newman J, Pathak R, Rehman A, Garnham A and Hobbs S. The role of compression after endovenous ablation of varicose veins. *J.Vasc.Surg.Venous Lymphat Disord.* 2018, 6:546-550
- Albanese G and Kondo K L. Pharmacology of sclerotherapy. *Semin.Intervent.Radiol.* 2010, 27:391-399
- Alder G and Lees T. Foam sclerotherapy. *Phlebology* 2015, 30:18-23
- Allegra C, Antignani P L and Carlizza A. Recurrent varicose veins following surgical treatment: our experience with five years follow-up. *Eur.J.Vasc.Endovasc.Surg.* 2007, 33:751-756
- Allegra C and Carlizza A. Oedema in Chronic Venous Insufficiency: Physiopathology and Investigation. *Phlebology* 2000, 15:122-125
- Almeida J I, Javier J J, Mackay E G, Bautista C, Cher D J and Proebstle T M. Thirty-sixth-month follow-up of first-in-human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:658-666
- Almeida J I, Javier J J, Mackay E, Bautista C and Proebstle T M. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *J.Vasc.Surg.Venous Lymphat Disord.* 2013, 1:174-180
- Anwar M A, Idrees M, Aswini M and Theivacumar N S. Fate of the tributaries of sapheno femoral junction following endovenous thermal ablation of incompetent axial vein - A review article. *Phlebology* 2019, 34:151-155

Anwar M A, Lane T R, Davies A H and Franklin I J. Complications of radiofrequency ablation of varicose veins. *Phlebology* 2012, 27 Suppl 1:34-39

Arslan U, Calik E, Tort M, Yildiz Z, Tekin A I, Limandal H K, Kaygin M A, Dag O and Erkut B. More Successful Results with Less Energy in Endovenous Laser Ablation Treatment: Long-term Comparison of Bare-tip Fiber 980 nm Laser and Radial-tip Fiber 1470 nm Laser Application. *Ann.Vasc.Surg.* 2017, 45:166-172

Austrell C, Thulin I and Norgren L. The Effects of Long Term Graduated Compression Treatment on Venous Function during Pregnancy. *Phlebology* 1995, 10:165-168

Baccellieri D, Ardita V, Carta N, Melissano G and Chiesa R. Anterior accessory saphenous vein confluence anatomy at the sapheno-femoral junction as risk factor for varicose veins recurrence after great saphenous vein radio-thermal-ablation. *Int.Angiol.* 2020,

Bainbridge D, Martin J, Arango M, Cheng D and Evidence-based Peri-operative Clinical Outcomes Research (EPiCOR) Group. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet* 2012, 380:1075-1081

Barron G S, Jacob S E and Kirsner R S. Dermatologic complications of chronic venous disease: medical management and beyond. *Ann.Vasc.Surg.* 2007, 21:652-662

Barwell J R, Davies C E, Deacon J, Harvey K, Minor J, Sassano A, Taylor M, Usher J, Wakely C, Earnshaw J J, Heather B P, Mitchell D C, Whyman M R and Poskitt K R. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet* 2004, 363:1854-1859

Beaglehole R, Prior I A, Salmond C E and Davidson F. Varicose veins in the South Pacific. *Int.J.Epidemiol.* 1975, 4:295-299

Beebe-Dimmer J L, Pfeifer J R, Engle J S and Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann.Epidemiol.* 2005, 15:175-184

Belramman A, Bootun R, Lane T R A and Davies A H. Foam sclerotherapy versus ambulatory phlebectomy for the treatment of varicose vein tributaries: study protocol for a randomised controlled trial. *Trials* 2019, 20:392-0

Belramman A, Bootun R, Tang T Y, Lane T R A and Davies A H. Mechanochemical ablation versus cyanoacrylate adhesive for the treatment of varicose veins: study protocol for a randomised controlled trial. *Trials* 2018, 19:428-0

Bergan J, Pascarella L and Mekenas L. Venous disorders: treatment with sclerosant foam. *J.Cardiovasc.Surg.(Torino)* 2006, 47:9-18

- Bergan J J, Schmid-Schonbein G W, Smith P D, Nicolaides A N, Boisseau M R and Eklof B. Chronic venous disease. *N.Engl.J.Med.* 2006, 355:488-498
- Beyer-Westendorf J, Schellong S M, Gerlach H, Rabe E, Weitz J I, Jersemann K, Sahin K, Bauersachs R and SURPRISE investigators. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. *Lancet Haematol.* 2017, 4:e105-e113
- Bhogal R H and Nyamekye I K. Should all patients undergo postoperative duplex imaging to detect a deep vein thrombosis after varicose vein surgery? *World J.Surg.* 2008, 32:237-240
- Boersma D, van Eekeren R R, Werson D A, van der Waal, R. I., Reijnen M M and de Vries J P. Mechanochemical endovenous ablation of small saphenous vein insufficiency using the ClariVein((R)) device: one-year results of a prospective series. *Eur.J.Vasc.Endovasc.Surg.* 2013, 45:299-303
- Boné C. Tratamiento endoluminal de las varices con laser de diodo: estudio preliminar. *Revista de patología vascular* 1999, 5:35-46
- Bootun R, Lane T R, Dharmarajah B, Lim C S, Najem M, Renton S, Sritharan K and Davies A H. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. *Phlebology* 2016, 31:61-65
- Bozkurt A K, Lawaetz M, Danielsson G, Lazaris A M, Pavlovic M, Olariu S and Rasmussen L. European College of Phlebology guideline for truncal ablation. *Phlebology* 2019, 268355519857362
- Bozkurt A K and Yilmaz M F. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. *Phlebology* 2016, 31:106-113
- Brand F N, Dannenberg A L, Abbott R D and Kannel W B. The epidemiology of varicose veins: the Framingham Study. *Am.J.Prev.Med.* 1988, 4:96-101
- Brittenden J, Cooper D, Dimitrova M, Scotland G, Cotton S C, Elders A, MacLennan G, Ramsay C R, Norrie J, Burr J M, Campbell B, Bachoo P, Chetter I, Gough M, Earnshaw J, Lees T, Scott J, Baker S A, Tassie E, Francis J and Campbell M K. Five-Year Outcomes of a Randomized Trial of Treatments for Varicose Veins. *N.Engl.J.Med.* 2019, 381:912-922
- Bruce A J, Bennett D D, Lohse C M, Rooke T W and Davis M D. Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. *J.Am.Acad.Dermatol.* 2002, 46:187-192

Buchtemann A S, Steins A, Volkert B, Hahn M, Klyszcz T and Junger M. The effect of compression therapy on venous haemodynamics in pregnant women. *Br.J.Obstet.Gynaecol.* 1999, 106:563-569

Byard R W and Gilbert J D. The incidence and characteristic features of fatal hemorrhage due to ruptured varicose veins: a 10-year autopsy study. *Am.J.Forensic Med.Pathol.* 2007, 28:299-302

Caggiati A, Phillips M, Lametschwandtner A and Allegra C. Valves in small veins and venules. *Eur.J.Vasc.Endovasc.Surg.* 2006, 32:447-452

Caggiati A, Bergan J J, Gloviczki P, Jantet G, Wendell-Smith C P, Partsch H and International Interdisciplinary Consensus Committee on Venous Anatomical Terminology. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J.Vasc.Surg.* 2002, 36:416-422

Calik E S, Arslan U and Erkut B. Ablation therapy with cyanoacrylate glue and laser for refluxing great saphenous veins - a prospective randomised study. *Vasa* 2019, 48:405-412

Callam M J. Epidemiology of varicose veins. *Br.J.Surg.* 1994, 81:167-173

Callam M J, Harper D R, Dale J J and Ruckley C V. Chronic ulcer of the leg: clinical history. *Br.Med.J.(Clin.Res.Ed)* 1987, 294:1389-1391

Campbell W B, Vijay Kumar A, Collin T W, Allington K L, Michaels J A and Randomised and Economic Analysis of Conservative and Therapeutic Interventions for Varicose veins Study. The outcome of varicose vein surgery at 10 years: clinical findings, symptoms and patient satisfaction. *Ann.R.Coll.Surg.Engl.* 2003, 85:52-57

Carpentier P H, Maricq H R, Biro C, Poncot-Makinen C O and Franco A. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: a population-based study in France. *J.Vasc.Surg.* 2004, 40:650-659

Carradice D. Superficial venous insufficiency from the infernal to the endothermal. *Ann.R.Coll.Surg.Engl.* 2014, 96:5-10

Cavezzi A and Parsi K. Complications of foam sclerotherapy. *Phlebology* 2012, 27 Suppl 1:46-51

Cavezzi A and Tessari L. Foam sclerotherapy techniques: different gases and methods of preparation, catheter versus direct injection. *Phlebology* 2009, 24:247-251

Cavezzi A, Labropoulos N, Partsch H, Ricci S, Caggiati A, Myers K, Nicolaidis A and Smith P C. Duplex ultrasound investigation of the veins in chronic venous disease of

- the lower limbs--UIP consensus document. Part II. Anatomy. Eur.J.Vasc.Endovasc.Surg. 2006, 31:288-299
- Chapman-Smith P and Browne A. Prospective five-year study of ultrasound-guided foam sclerotherapy in the treatment of great saphenous vein reflux. Phlebology 2009, 24:183-188
- Chen S S and Prasad S K. Long saphenous vein and its anatomical variations. Australas.J.Ultrasound Med. 2009, 12:28-31
- Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A and Cavezzi A. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs--UIP consensus document. Part I. Basic principles. Eur.J.Vasc.Endovasc.Surg. 2006, 31:83-92
- Connor D E, Joseph J E, Exner T, Ma D D and Parsi K. Infusion of foam sclerosants results in a distance-dependent procoagulant activity, haemoconcentration and elevation of D-dimer levels. Phlebology 2014, 29:677-687
- Coon W W, Willis P W, 3rd and Keller J B. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation 1973, 48:839-846
- Crawford J M, Lal B K, Duran W N and Pappas P J. Pathophysiology of venous ulceration. J.Vasc.Surg.Venous Lymphat Disord. 2017, 5:596-605
- Criqui M H, Jamosmos M, Fronck A, Denenberg J O, Langer R D, Bergan J and Golomb B A. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. Am.J.Epidemiol. 2003, 158:448-456
- Critchley G, Handa A, Maw A, Harvey A, Harvey M R and Corbett C R. Complications of varicose vein surgery. Ann.R.Coll.Surg.Engl. 1997, 79:105-110
- Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society for Vascular Surgery. Venous insufficiency: Current Care Guidelines. 2016.
- da Silva A, Widmer L K, Martin H, Mall T, Glaus L and Schneider M. Varicose veins and chronic venous insufficiency. Vasa 1974, 3:118-125
- De Maeseneer M, Pichot O, Cavezzi A, Earnshaw J, van Rij A, Lurie F, Smith P C and Union Internationale de Phlebologie. Duplex ultrasound investigation of the veins of the lower limbs after treatment for varicose veins - UIP consensus document. Eur.J.Vasc.Endovasc.Surg. 2011, 42:89-102

de Medeiros C A and Luccas G C. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. *Dermatol.Surg.* 2005, 31:1685-94; discussion 1694

de Mik S M, Stubenrouch F E, Legemate D A, Balm R and Ubbink D T. Treatment of varicose veins, international consensus on which major complications to discuss with the patient: A Delphi study. *Phlebology* 2019, 34:201-207

de Palma R G, Hart M T, Zanin L and Massarin E H. Physical Examination, Doppler Ultrasound and Colour Flow Duplex Scanning: Guides to Therapy for Primary Varicose Veins.1993, 8:7-11

Deijen C L, Schreve M A, Bosma J, de Nie A J, Leijdekkers V J, van den Akker, P. J. and Vahl A. Clarivein mechanochemical ablation of the great and small saphenous vein: Early treatment outcomes of two hospitals. *Phlebology* 2016, 31:192-197

Dermody M, O'Donnell T F and Balk E M. Complications of endovenous ablation in randomized controlled trials. *J.Vasc.Surg.Venous Lymphat Disord.* 2013, 1:427-436.e1

Di Nisio M, Wichers I M and Middeldorp S. Treatment for superficial thrombophlebitis of the leg. *Cochrane Database Syst.Rev.* 2018, 2:CD004982

Disselhoff B C, der Kinderen D J, Kelder J C and Moll F L. Five-year results of a randomized clinical trial comparing endovenous laser ablation with cryostripping for great saphenous varicose veins. *Br.J.Surg.* 2011a, 98:1107-1111

Disselhoff B C, der Kinderen D J, Kelder J C and Moll F L. Five-year results of a randomised clinical trial of endovenous laser ablation of the great saphenous vein with and without ligation of the saphenofemoral junction. *Eur.J.Vasc.Endovasc.Surg.* 2011b, 41:685-690

Disselhoff B C, Rem A I, Verdaasdonk R M, Kinderen D J and Moll F L. Endovenous laser ablation: an experimental study on the mechanism of action. *Phlebology* 2008, 23:69-76

Disselhoff B C, der Kinderen D J and Moll F L. Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment? *J.Endovasc.Ther.* 2005, 12:731-738

Dwerryhouse S, Davies B, Harradine K and Earnshaw J J. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. *J.Vasc.Surg.* 1999, 29:589-592

Eberhardt R T and Raffetto J D. Chronic venous insufficiency. *Circulation* 2014, 130:333-346

Eklof B, Rutherford R B, Bergan J J, Carpentier P H, Gloviczki P, Kistner R L, Meissner M H, Moneta G L, Myers K, Padberg F T, Perrin M, Ruckley C V, Smith P C, Wakefield T W and 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, 40:1248-1252

Elias S, Lam Y L and Wittens C H. Mechanochemical ablation: status and results. *Phlebology* 2013, 28 Suppl 1:10-14

Elias S and Raines J K. Mechanochemical tumescentless endovenous ablation: final results of the initial clinical trial. *Phlebology* 2012, 27:67-72

Enkin M, Keirse M, Neilson J, Crowther C, Duley L, Hodnett E, Enkin M, Keirse M, Neilson J and Crowther C. Unpleasant symptoms in pregnancy. A Guide to effective care in pregnancy and childbirth 2000, 95:107

Epstein D, Onida S, Bootun R, Ortega-Ortega M and Davies A H. Cost-Effectiveness of Current and Emerging Treatments of Varicose Veins. *Value Health.* 2018, 21:911-920

Evans C J, Fowkes F G, Ruckley C V and Lee A J. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J.Epidemiol.Community Health* 1999, 53:149-153

Fan C M and Rox-Anderson R. Endovenous laser ablation: mechanism of action. *Phlebology* 2008, 23:206-213

Fegan W G. Continuous compression technique of injecting varicose veins. *Lancet* 1963, 2:109-112

Flessenkamper I, Hartmann M, Hartmann K, Stenger D and Roll S. Endovenous laser ablation with and without high ligation compared to high ligation and stripping for treatment of great saphenous varicose veins: Results of a multicentre randomised controlled trial with up to 6 years follow-up. *Phlebology* 2016a, 31:23-33

Flessenkamper I, Hartmann M, Hartmann K, Stenger D and Roll S. Endovenous laser ablation with and without high ligation compared to high ligation and stripping for treatment of great saphenous varicose veins: Results of a multicentre randomised controlled trial with up to 6 years follow-up. *Phlebology* 2016b, 31:23-33

Franks P J, Wright D D, Moffatt C J, Stirling J, Fletcher A E, Bulpitt C J and McCollum C N. Prevalence of venous disease: a community study in west London. *Eur.J.Surg.* 1992, 158:143-147

Frappe P, Buchmuller-Cordier A, Bertoletti L, Bonithon-Kopp C, Couzan S, Lafond P, Leizorovicz A, Merah A, Presles E, Preynat P, Tardy B, Decousus H and STEPH Study

Group. Annual diagnosis rate of superficial vein thrombosis of the lower limbs: the STEPH community-based study. *J.Thromb.Haemost.* 2014, 12:831-838

Frings N, Glowacki P and Kohajda J. Major vascular and neural complications in varicose vein surgery. Prospective documentation of complication rate in surgery of the V. saphena magna and V. saphena parva. *Chirurg* 2001, 72:1032-1035

Fronek A. Photoplethysmography in the diagnosis of venous disease. *Dermatol.Surg.* 1995, 21:64-66

Garcia R and Labropoulos N. Duplex Ultrasound for the Diagnosis of Acute and Chronic Venous Diseases. *Surg.Clin.North Am.* 2018, 98:201-218

Garratt A M, Ruta D A, Abdalla M I and Russell I T. Responsiveness of the SF-36 and a condition-specific measure of health for patients with varicose veins. *Qual.Life Res.* 1996, 5:223-234

Garratt A M, Macdonald L M, Ruta D A, Russell I T, Buckingham J K and Krukowski Z H. Towards measurement of outcome for patients with varicose veins. *Qual.Health Care* 1993a, 2:5-10

Garratt A M, Macdonald L M, Ruta D A, Russell I T, Buckingham J K and Krukowski Z H. Towards measurement of outcome for patients with varicose veins. *Qual.Health Care* 1993b, 2:5-10

Gibson K, Minjarez R, Gunderson K and Ferris B. Need for adjunctive procedures following cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of postprocedure compression: Three-month data from a postmarket evaluation of the VenaSeal System (the WAVES Study). *Phlebology* 2019, 34:231-237

Gillet J and for the Guideline Group. Complications and side effects: European Guidelines for Sclerotherapy in Chronic Venous Disorders. *Phlebology* 2014, 29:34-38

Goldman M P, Sadick N S and Weiss R A. Cutaneous necrosis, telangiectatic matting, and hyperpigmentation following sclerotherapy. Etiology, prevention, and treatment. *Dermatol.Surg.* 1995, 21:19-2

Goodyear S J and Nyamekye I K. Radiofrequency ablation of varicose veins: Best practice techniques and evidence. *Phlebology* 2015, 30:9-17

Goulart V B, Cabral A C, Reis Z S, Navarro T P, Alves S L, de Miranda P R, Sarquis A L and de Lima Rezende, C. A. Anatomical and physiological changes in the venous system of lower limbs in pregnant women and findings associated with the symptomatology. *Arch.Gynecol.Obstet.* 2013, 288:73-78

- Greitz T. The technique of ascending phlebography of the lower extremity. *Acta Radiol.* 1954, 42:421-441
- Guberan E, Widmer L K, Glaus L, Muller R, Rougemont A, Da Silva A and Gendre F. Causative factors of varicose veins: myths and facts. An epidemiological study of 610 women. *Vasa* 1973, 2:115-120
- Hager E S, Ozvath K J and Dillavou E D. Evidence summary of combined saphenous ablation and treatment of varicosities versus staged phlebectomy. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:134-137
- Hamel-Desnos C M, Guias B J, Desnos P R and Mesgard A. Foam sclerotherapy of the saphenous veins: randomised controlled trial with or without compression. *Eur.J.Vasc.Endovasc.Surg.* 2010, 39:500-507
- Harris M and Chung F. Complications of general anesthesia. *Clin.Plast.Surg.* 2013, 40:503-513
- Hassanin A, Aherne T M, Greene G, Boyle E, Egan B, Tierney S, Walsh S R, McHugh S and Aly S. A systematic review and meta-analysis of comparative studies comparing nonthermal versus thermal endovenous ablation in superficial venous incompetence. *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:902-913.e3
- He G, Zheng C, Yu M A and Zhang H. Comparison of ultrasound-guided endovenous laser ablation and radiofrequency for the varicose veins treatment: An updated meta-analysis. *Int.J.Surg.* 2017, 39:267-275
- Healy D A, Kimura S, Power D, Elhaj A, Abdeldaim Y, Cross K S, McGreal G T, Burke P E, Moloney T, Manning B J and Kavanagh E G. A Systematic Review and Meta-analysis of Thrombotic Events Following Endovenous Thermal Ablation of the Great Saphenous Vein. *Eur.J.Vasc.Endovasc.Surg.* 2018, 56:410-424
- Helmy ElKaffas K, ElKashef O and ElBaz W. Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins-a randomized clinical trial. *Angiology* 2011, 62:49-54
- Hicks C W, DiBrito S R, Magruder J T, Weaver M L, Barenski C and Heller J A. Radiofrequency ablation with concomitant stab phlebectomy increases risk of endovenous heat-induced thrombosis. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:200-209
- Hirai M, Naiki K and Nakayama R. Prevalence and risk factors of varicose veins in Japanese women. *Angiology* 1990, 41:228-232
- Hirokawa M, Ogawa T, Sugawara H, Shokoku S and Sato S. Comparison of 1470 nm Laser and Radial 2ring Fiber with 980 nm Laser and Bare-Tip Fiber in Endovenous

Laser Ablation of Saphenous Varicose Veins: A Multicenter, Prospective, Randomized, Non-Blind Study. *Ann.Vasc.Dis.* 2015, 8:282-289

Hirokawa M and Kurihara N. Comparison of Bare-Tip and Radial Fiber in Endovenous Laser Ablation with 1470 nm Diode Laser. *Ann.Vasc.Dis.* 2014, 7:239-245

Hirsch T. Varicose vein therapy and nerve lesions. *Vasa* 2017, 46:96-100

Holewijn S, van Eekeren, R. R. J. P., Vahl A, de Vries, J. P. P. M., Reijnen, M. M. P. J. and MARADONA study group. Two-year results of a multicenter randomized controlled trial comparing Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial). *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:364-374

Holme K, Matzen M, Bomberg A J, Outzen S L and Holme J B. Partial or total stripping of the great saphenous vein. 5-year recurrence frequency and 3-year frequency of neural complications after partial and total stripping of the great saphenous vein. *Ugeskr.Laeger* 1996, 158:405-408

Holt N F. Tumescant anaesthesia: its applications and well tolerated use in the out-of-operating room setting. *Curr.Opin.Anaesthesiol.* 2017, 30:518-524

Ismail L, Normahani P, Standfield N J and Jaffer U. A systematic review and meta-analysis of the risk for development of varicose veins in women with a history of pregnancy. *J.Vasc.Surg.Venous Lymphat Disord.* 2016, 4:518-524.e1

Jacobs B N, Andraska E A, Obi A T and Wakefield T W. Pathophysiology of varicose veins. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:460-467

Jaworucka-Kaczorowska A, Oszkinis G, Huber J, Wiertel-Krawczuk A, Gabor E and Kaczorowski P. Saphenous vein stripping surgical technique and frequency of saphenous nerve injury. *Phlebology* 2015, 30:210-216

Jia X, Mowatt G, Burr J M, Cassar K, Cook J and Fraser C. Systematic review of foam sclerotherapy for varicose veins. *Br.J.Surg.* 2007, 94:925-936

Jones A D, Boyle E M, Woltjer R, Jundt J P and Williams A N. Persistent type IV hypersensitivity after cyanoacrylate closure of the great saphenous vein. *J.Vasc.Surg.Cases Innov.Tech.* 2019, 5:372-374

Jones L, Braithwaite B D, Selwyn D, Cooke S and Earnshaw J J. Neovascularisation is the principal cause of varicose vein recurrence: results of a randomised trial of stripping the long saphenous vein. *Eur.J.Vasc.Endovasc.Surg.* 1996, 12:442-445

- Kabnick, H. Agis, M. Moritz and S. Giorgio. Endovenous heat induced thrombus (EHIT) following endovenous vein obliteration: to treat or not to treat. A new thrombotic classification. 2005 3rd International Vein Congress April 14-16, 2005 Miami, FL
- Kahn S R, M'lan C E, Lamping D L, Kurz X, Berard A, Abenhaim L A and VEINES Study Group. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. *J.Vasc.Surg.* 2004, 39:823-828
- Kalodiki E, Lattimer C R, Azzam M, Shawish E, Bountouroglou D and Geroulakos G. Long-term results of a randomized controlled trial on ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation vs standard surgery for varicose veins. *J.Vasc.Surg.* 2012, 55:451-457
- Kankam H K N, Lim C S, Fiorentino F, Davies A H and Gohel M S. A Summation Analysis of Compliance and Complications of Compression Hosiery for Patients with Chronic Venous Disease or Post-thrombotic Syndrome. *Eur.J.Vasc.Endovasc.Surg.* 2018, 55:406-416
- Kim P S, Bishawi M, Draughn D, Boter M, Gould C, Koziarski J, Bernstein R and Hamilton R. Mechanochemical ablation for symptomatic great saphenous vein reflux: A two-year follow-up. *Phlebology* 2017, 32:43-48
- Kim S Y, Safir S R, Png C Y M, Faries P L, Ting W, Vouyouka A G, Marin M L and Tadros R O. Mechanochemical ablation as an alternative to venous ulcer healing compared with thermal ablation. *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:699-705
- Kistner R L and Kamida C B. 1994 Update on Phlebography and Varicography. *Dermatol.Surg.* 1995, 21:71-76
- Kontosic I, Vukelic M, Drescik I, Mesaros-Kanjski E, Materljan E and Jonjic A. Work conditions as risk factors for varicose veins of the lower extremities in certain professions of the working population of Rijeka. *Acta Med.Okayama* 2000, 54:33-38
- Koramaz I, El Kilic H, Gokalp F, Bitargil M, Bektas N, Engin E, Egici M T and Bozkurt A K. Ablation of the great saphenous vein with nontumescent n-butyl cyanoacrylate versus endovenous laser therapy. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:210-215
- Kostas T, Ioannou C V, Touloupakis E, Daskalaki E, Giannoukas A D, Tsetis D and Katsamouris A N. Recurrent varicose veins after surgery: a new appraisal of a common and complex problem in vascular surgery. *Eur.J.Vasc.Endovasc.Surg.* 2004, 27:275-282

Kulkarni S R, Messenger D E, Slim F J, Emerson L G, Bulbulia R A, Whyman M R and Poskitt K R. The incidence and characterization of deep vein thrombosis following ultrasound-guided foam sclerotherapy in 1000 legs with superficial venous reflux. *J.Vasc.Surg.Venous Lymphat Disord.* 2013, 1:231-238

Labropoulos N, Tiongson J, Pryor L, Tassiopoulos A K, Kang S S, Ashraf Mansour M and Baker W H. Definition of venous reflux in lower-extremity veins. *J.Vasc.Surg.* 2003, 38:793-798

Labropoulos N, Tassiopoulos A K, Kang S S, Mansour M A, Littooy F N and Baker W H. Prevalence of deep venous reflux in patients with primary superficial vein incompetence. *J.Vasc.Surg.* 2000, 32:663-668

Ladwig A, Haase H, Bichel J, Schuren J and Junger M. Compression therapy of leg ulcers with PAOD. *Phlebology* 2014, 29:7-12

Lam Y L, Toonder I M and Wittens C H. Clarivein(R) mechano-chemical ablation an interim analysis of a randomized controlled trial dose-finding study. *Phlebology* 2016, 31:170-176

Lane T R, Bootun R, Dharmarajah B, Lim C S, Najem M, Renton S, Sritharan K and Davies A H. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. *Phlebology* 2017, 32:89-98

Lane T R, Kelleher D, Shepherd A C, Franklin I J and Davies A H. Ambulatory varicosity avulsion later or synchronized (AVULS): a randomized clinical trial. *Ann.Surg.* 2015, 261:654-661

Lane T R, Moore H M, Franklin I J and Davies A H. Retrograde inversion stripping as a complication of the ClariVein mechanochemical venous ablation procedure. *Ann.R.Coll.Surg.Engl.* 2015, 97:18

Lascaratos J, Liapis C and Kouvaraki M. Surgery on varices in Byzantine times (324-1453 CE). *J.Vasc.Surg.* 2001, 33:197-203

Lattimer C R, Azzam M, Kalodiki E and Geroulakos G. Venous filling time using air-plethysmography correlates highly with great saphenous vein reflux time using duplex. *Phlebology* 2014, 29:90-97

Laurikka J O, Sisto T, Tarkka M R, Auvinen O and Hakama M. Risk indicators for varicose veins in forty- to sixty-year-olds in the Tampere varicose vein study. *World J Surg.* 2002, 26:648-51

Laurikka J, Laara E, Sisto T, Tarkka M, Auvinen O and Hakama M. Misclassification in a questionnaire survey of varicose veins. *J.Clin.Epidemiol.* 1995, 48:1175-1178

- Lawaetz M, Serup J, Lawaetz B, Bjoern L, Blemings A, Eklof B and Rasmussen L. Comparison of endovenous ablation techniques, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Extended 5-year follow-up of a RCT. *Int.Angiol.* 2017a, 36:281-288
- Lawaetz M, Serup J, Lawaetz B, Bjoern L, Blemings A, Eklof B and Rasmussen L. Comparison of endovenous ablation techniques, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Extended 5-year follow-up of a RCT. *Int.Angiol.* 2017b, 36:281-288
- Lawson J, Gauw S, van Vlijmen C, Pronk P, Gaastra M, Mooij M and Wittens C H. Saphen: the solution? *Phlebology* 2013, 28 Suppl 1:2-9
- Lee A J, Evans C J, Allan P L, Ruckley C V and Fowkes F G. Lifestyle factors and the risk of varicose veins: Edinburgh Vein Study. *J.Clin.Epidemiol.* 2003, 56:171-179
- Leon L, Giannoukas A D, Dodd D, Chan P and Labropoulos N. Clinical significance of superficial vein thrombosis. *Eur.J.Vasc.Endovasc.Surg.* 2005, 29:10-17
- Lim C S and Davies A H. Pathogenesis of primary varicose veins. *Br.J.Surg.* 2009, 96:1231-1242
- Lim S Y, Tan J X, D'Cruz R T, Syn N, Chong T T and Tang T Y. Catheter-directed foam sclerotherapy, an alternative to ultrasound-guided foam sclerotherapy for varicose vein treatment: A systematic review and meta-analysis. *Phlebology* 2020,
- Lohr J and Kulwicki A. Radiofrequency ablation: evolution of a treatment. *Semin.Vasc.Surg.* 2010, 23:90-100
- Lurie F, Comerota A, Eklof B, Kistner R L, Labropoulos N, Lohr J, Marston W, Meissner M, Moneta G, Neglen P, Neuhardt D, Padberg F, Jr and Welsh H J. Multicenter assessment of venous reflux by duplex ultrasound. *J.Vasc.Surg.* 2012, 55:437-445
- Lurie F, Creton D, Eklof B, Kabnick L S, Kistner R L, Pichot O, Sessa C and Schuller-Petrovic S. Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVEs): two-year follow-up. *Eur.J.Vasc.Endovasc.Surg.* 2005, 29:67-73
- Lurie F, Creton D, Eklof B, Kabnick L S, Kistner R L, Pichot O, Schuller-Petrovic S and Sessa C. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVEs Study). *J.Vasc.Surg.* 2003, 38:207-214
- Lurie F, Kistner R L and Eklof B. The mechanism of venous valve closure in normal physiologic conditions. *J.Vasc.Surg.* 2002, 35:713-717

Maessen-Visch M B, Koedam M I, Hamulyak K and Neumann H A. Atrophie blanche. *Int.J.Dermatol.* 1999, 38:161-172

Maffei F H, Magaldi C, Pinho S Z, Lastoria S, Pinho W, Yoshida W B and Rollo H A. Varicose veins and chronic venous insufficiency in Brazil: prevalence among 1755 inhabitants of a country town. *Int.J.Epidemiol.* 1986, 15:210-217

Malskat W S, Poluektova A A, van der Geld, C. W., Neumann H A, Weiss R A, Bruijninx C M and van Gemert M J. Endovenous laser ablation (EVLA): a review of mechanisms, modeling outcomes, and issues for debate. *Lasers Med.Sci.* 2014, 29:393-403

Malskat W S J, Engels L K, Hollestein L M, Nijsten T and van den Bos, R. R. Commonly Used Endovenous Laser Ablation (EVLA) Parameters Do Not Influence Efficacy: Results of a Systematic Review and Meta-Analysis. *Eur.J.Vasc.Endovasc.Surg.* 2019, 58:230-242

Marsden G, Perry M, Kelley K, Davies A H and Guideline Development Group. Diagnosis and management of varicose veins in the legs: summary of NICE guidance. *BMJ* 2013, 347:f4279

Maurins U, Hoffmann B H, Losch C, Jockel K H, Rabe E and Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population--results from the Bonn Vein Study, Germany. *J.Vasc.Surg.* 2008, 48:680-687

McGuinness B, Elias F, Ali K P, Ahmad M S, Namburi J, Chan B, Szalay D and Rapanos T. A comparison of duplex ultrasound findings after cyanoacrylate embolization versus endovenous laser ablation of the great saphenous vein. *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:824-831

Meissner M H. Lower extremity venous anatomy. *Semin.Intervent.Radiol.* 2005, 22:147-156

Meissner M H, Natiello C and Nicholls S C. Performance characteristics of the venous clinical severity score. *J.Vasc.Surg.* 2002, 36:889-895

Mekky S, Schilling R S and Walford J. Varicose veins in women cotton workers. An epidemiological study in England and Egypt. *Br.Med.J.* 1969, 2:591-595

Mendes-Pinto D, Bastianetto P, Cavalcanti Braga Lyra L, Kikuchi R and Kabnick L. Endovenous laser ablation of the great saphenous vein comparing 1920-nm and 1470-nm diode laser. *Int.Angiol.* 2016, 35:599-604

Merrett N D and Hanel K C. Ischaemic complications of graduated compression stockings in the treatment of deep venous thrombosis. *Postgrad.Med.J.* 1993, 69:232-234

- Michaels J A, Campbell W B, Brazier J E, Macintyre J B, Palfreyman S J, Ratcliffe J and Rigby K. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol.Assess.* 2006, 10:1-iv
- Miller G V, Lewis W G, Sainsbury J R and Macdonald R C. Morbidity of varicose vein surgery: auditing the benefit of changing clinical practice. *Ann.R.Coll.Surg.Engl.* 1996, 78:345-349
- Milleret R, Huot L, Nicolini P, Creton D, Roux A S, Decullier E, Chapuis F R and Camelot G. Great saphenous vein ablation with steam injection: results of a multicentre study. *Eur.J.Vasc.Endovasc.Surg.* 2013, 45:391-396
- Min R J, Khilnani N and Zimmet S E. Endovenous laser treatment of saphenous vein reflux: long-term results. *J.Vasc.Interv.Radiol.* 2003, 14:991-996
- Min R J, Zimmet S E, Isaacs M N and Forrestal M D. Endovenous laser treatment of the incompetent greater saphenous vein. *J.Vasc.Interv.Radiol.* 2001, 12:1167-1171
- Miteva M, Romanelli P and Kirsner R S. Lipodermatosclerosis. *Dermatol.Ther.* 2010, 23:375-388
- Mlosek R K, Wozniak W, Gruszecki L and Stapa R Z. The use of a novel method of endovenous steam ablation in treatment of great saphenous vein insufficiency: own experiences. *Phlebology* 2014, 29:58-65
- Moore W. The operative treatment of varicose veins, with especial reference to a modification of Trendelenburg's operation. *Intercolonial Medical Journal of Australasia* 1896, 1:393-407
- Morrison C and Dalsing M C. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity, and relevance for modern practice. *J.Vasc.Surg.* 2003, 38:886-890
- Morrison N, Kolluri R, Vasquez M, Madsen M, Jones A and Gibson K. Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36-Month outcomes of the VeClose randomized controlled trial. *Phlebology* 2019, 34:380-390
- Mueller R L and Raines J K. ClariVein mechanochemical ablation: background and procedural details. *Vasc.Endovascular Surg.* 2013, 47:195-206
- Myers K A and Jolley D. Factors affecting the risk of deep venous occlusion after ultrasound-guided sclerotherapy for varicose veins. *Eur.J.Vasc.Endovasc.Surg.* 2008, 36:602-605

Nasr H and Scriven J M. Superficial thrombophlebitis (superficial venous thrombosis). *BMJ* 2015, 350:h2039

Nasser H, Ivanics T, Shakaroun D and Lin J. Severe phlebitis-like abnormal reaction following great saphenous vein cyanoacrylate closure. *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:578-582

Navarro L, Min R J and Bone C. Endovenous laser: a new minimally invasive method of treatment for varicose veins--preliminary observations using an 810 nm diode laser. *Dermatol.Surg.* 2001, 27:117-122

Nilsson L, Austrell C and Norgren L. Venous function during late pregnancy, the effect of elastic compression hosiery. *Vasa* 1992, 21:203-205

Nordon I M, Hinchliffe R J, Brar R, Moxey P, Black S A, Thompson M M and Loftus I M. A prospective double-blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins. *Ann.Surg.* 2011, 254:876-881

Nyamekye I, Shephard N A, Davies B, Heather B P and Earnshaw J J. Clinicopathological evidence that neovascularisation is a cause of recurrent varicose veins. *Eur.J.Vasc.Endovasc.Surg.* 1998, 15:412-415

Nyamekye I K. A practical approach to tumescent local anaesthesia in ambulatory endovenous thermal ablation. *Phlebology* 2019, 34:238-245

Nyamekye I K, Dattani N, Hayes W, Harding D, Holloway S and Newman J. A Randomised Controlled Trial Comparing Three Different Radiofrequency Technologies: Short-Term Results of the 3-RF Trial. *Eur.J.Vasc.Endovasc.Surg.* 2019, 58:401-408

Obermayer. Technique and preliminary results of HIFU for varicose veins. 2019 Charing Cross Vascular Symposium 15.-18.4.2019 London, UK

O'Donnell T F, Balk E M, Dermody M, Tangney E and Iafrati M D. Recurrence of varicose veins after endovenous ablation of the great saphenous vein in randomized trials. *J.Vasc.Surg.Venous Lymphat Disord.* 2016, 4:97-105

O'Donnell T F, Eaddy M, Raju A, Boswell K and Wright D. Assessment of thrombotic adverse events and treatment patterns associated with varicose vein treatment. *J.Vasc.Surg.Venous Lymphat Disord.* 2015, 3:27-34

Onida S and Davies A H. Predicted burden of venous disease. *Phlebology* 2016, 31:74-79

Onida S and Davies A H. CHIVA, ASVAL and related techniques--Concepts and evidence. *Phlebology* 2015, 30:42-45

- Ostler A E, Holdstock J M, Harrison C C, Price B A and Whiteley M S. Strip-tract revascularization as a source of recurrent venous reflux following high saphenous tie and stripping: results at 5-8 years after surgery. *Phlebology* 2015, 30:569-572
- Ovali C and Sevin M B. Twelve-month efficacy and complications of cyanoacrylate embolization compared with radiofrequency ablation for incompetent great saphenous veins. *J.Vasc.Surg.Venous Lymphat Disord.* 2019, 7:210-216
- Palfreyman S J and Michaels J A. A systematic review of compression hosiery for uncomplicated varicose veins. *Phlebology* 2009, 24 Suppl 1:13-33
- Pan Y, Zhao J, Mei J, Shao M and Zhang J. Comparison of endovenous laser ablation and high ligation and stripping for varicose vein treatment: a meta-analysis. *Phlebology* 2014, 29:109-119
- Park I, Jeong M H, Park C J, Park W I, Park D W and Joh J H. Clinical Features and Management of "Phlebitis-like Abnormal Reaction" After Cyanoacrylate Closure for the Treatment of Incompetent Saphenous Veins. *Ann.Vasc.Surg.* 2019, 55:239-245
- Parsi K, Kang M, Yang A and Kossard S. Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation. *Phlebology* 2019, 268355519856756
- Parsi K, Roberts S, Kang M, Benson S, Baker L, Berman I, Bester L J, Connor D E, Dinnen P, Grace J, Stirling A, Ibrahim N, Lekich C, Lim A, Matar L, Nadkarni S, Paraskevas P, Rogan C, Thibault P K, Thibault S, van Rij A and Yang A. Cyanoacrylate closure for peripheral veins: Consensus document of the Australasian College of Phlebology. *Phlebology* 2019, 268355519864755
- Parsi K. Paradoxical embolism, stroke and sclerotherapy. *Phlebology* 2012, 27:147-167
- Partsch H, Clark M, Mosti G, Steinlechner E, Schuren J, Abel M, Benigni J P, Coleridge-Smith P, Cornu-Thenard A, Flour M, Hutchinson J, Gamble J, Issberner K, Juenger M, Moffatt C, Neumann H A, Rabe E, Uhl J F and Zimmet S. Classification of compression bandages: practical aspects. *Dermatol.Surg.* 2008, 34:600-609
- Perala J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T and Juvonen T. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. *Ann.Vasc.Surg.* 2005, 19:669-672
- Perkowski P, Ravi R, Gowda R C, Olsen D, Ramaiah V, Rodriguez-Lopez J A and Diethrich E B. Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single-center experience. *J.Endovasc.Ther.* 2004, 11:132-138

Perrin M, Dedieu F, Jessent V and Blanc M. Evaluation of the new severity scoring system in chronic venous disease of the lower limbs: an observational study conducted by French angiologists. 2006, 13:6-16

Perrot-Applanat M, Cohen-Solal K, Milgrom E and Finet M. Progesterone receptor expression in human saphenous veins. *Circulation* 1995, 92:2975-2983

Pichot O, Kabnick L S, Creton D, Merchant R F, Schuller-Petroviae S and Chandler J G. Duplex ultrasound scan findings two years after great saphenous vein radiofrequency endovenous obliteration. *J.Vasc.Surg.* 2004, 39:189-195

Pichot O, Sessa C, Chandler J G, Nuta M and Perrin M. Role of duplex imaging in endovenous obliteration for primary venous insufficiency. *J.Endovasc.Ther.* 2000, 7:451-459

Pitkanen M T, Aromaa U, Cozanitis D A and Forster J G. Serious complications associated with spinal and epidural anaesthesia in Finland from 2000 to 2009. *Acta Anaesthesiol.Scand.* 2013, 57:553-564

Politowski M and Zelazny T. Complications and difficulties associated with electrocoagulation treatment of varices of lower extremities. *Pol.Przegl.Chir.* 1966, 38:519-522

Porter J M and Moneta G L. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J.Vasc.Surg.* 1995, 21:635-645

Proebstle T and van den Bos R. Endovenous ablation of refluxing saphenous and perforating veins. *Vasa* 2017, 46:159-166

Rabe E, Partsch H, Morrison N, Meissner M H, Mosti G, Lattimer C R, Carpentier P H, Gaillard S, Junger M, Urbanek T, Hafner J, Patel M, Wu S, Caprini J, Lurie F and Hirsch T. Risks and contraindications of medical compression treatment - A critical reappraisal. An international consensus statement. *Phlebology* 2020, 268355520909066

Rabe E, Breu F X, Cavezzi A, Coleridge Smith P, Frullini A, Gillet J L, Guex J J, Hamel-Desnos C, Kern P, Partsch B, Ramelet A A, Tessari L, Pannier F and Guideline Group. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology* 2014, 29:338-354

Rabe E, Guex J J, Puskas A, Scuderi A, Fernandez Quesada F and VCP Coordinators. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. *Int.Angiol.* 2012, 31:105-115

Radak D, Djukic N and Neskovic M. Cyanoacrylate Embolization: A Novelty in the Field of Varicose Veins Surgery. *Ann.Vasc.Surg.* 2019, 55:285-291

- Raju S, Lurie F and O'Donnell T F, Jr. Compression use in the era of endovenous interventions and wound care centers. *J.Vasc.Surg.Venous Lymphat Disord.* 2016, 4:346-354
- Rasmussen L, Lawaetz M, Bjoern L, Blemings A and Eklof B. Randomized clinical trial comparing endovenous laser ablation and stripping of the great saphenous vein with clinical and duplex outcome after 5 years. *J.Vasc.Surg.* 2013, 58:421-426
- Rasmussen L H, Bjoern L, Lawaetz M, Lawaetz B, Blemings A and Eklof B. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. *Eur.J.Vasc.Endovasc.Surg.* 2010, 39:630-635
- Rasmussen L H, Bjoern L, Lawaetz M, Blemings A, Lawaetz B and Eklof B. Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short-term results. *J.Vasc.Surg.* 2007, 46:308-315
- Rass K, Frings N, Glowacki P, Graber S, Tilgen W and Vogt T. Same Site Recurrence is More Frequent After Endovenous Laser Ablation Compared with High Ligation and Stripping of the Great Saphenous Vein: 5 year Results of a Randomized Clinical Trial (RELACS Study). *Eur.J.Vasc.Endovasc.Surg.* 2015, 50:648-656
- Rautio T, Perala J, Biancari F, Wiik H, Ohtonen P, Haukipuro K and Juvonen T. Accuracy of hand-held Doppler in planning the operation for primary varicose veins. *Eur.J.Vasc.Endovasc.Surg.* 2002, 24:450-455
- Ravi R, Rodriguez-Lopez J A, Trayler E A, Barrett D A, Ramaiah V and Diethrich E B. Endovenous ablation of incompetent saphenous veins: a large single-center experience. *J.Endovasc.Ther.* 2006, 13:244-248
- Recek C. Competent and incompetent calf perforators in primary varicose veins: a resistant myth. *Phlebology* 2016, 31:532-540
- Ricci S and Caggiati A. Echoanatomical Patterns of the Long Saphenous Vein in Patients with Primary Varices and in Healthy Subjects. *Phlebology* 1999, 54-58
- Richardson J B and Dixon M. Varicose veins in tropical Africa. *Lancet* 1977, 1:791-792
- Robertson L, Evans C and Fowkes F G. Epidemiology of chronic venous disease. *Phlebology* 2008, 23:103-111
- Ropacka-Lesiak M, Kasperczak J and Breborowicz G H. Risk factors for the development of venous insufficiency of the lower limbs during pregnancy--part 1. *Ginekol.Pol.* 2012, 83:939-942

Royle J and Somjen G M. Varicose veins: Hippocrates to Jerry Moore. ANZ J.Surg. 2007, 77:1120-1127

Ruckley C V, Evans C J, Allan P L, Lee A J and Fowkes F G. Telangiectasia in the Edinburgh Vein Study: epidemiology and association with trunk varices and symptoms. Eur.J.Vasc.Endovasc.Surg. 2008, 36:719-724

Ruckley C V, Evans C J, Allan P L, Lee A J and Fowkes F G. Chronic venous insufficiency: clinical and duplex correlations. The Edinburgh Vein Study of venous disorders in the general population. J.Vasc.Surg. 2002, 36:520-525

Rutherford R B, Padberg F T,Jr, Comerota A J, Kistner R L, Meissner M H and Moneta G L. Venous severity scoring: An adjunct to venous outcome assessment. J.Vasc.Surg. 2000a, 31:1307-1312

Rutherford R B, Padberg F T,Jr, Comerota A J, Kistner R L, Meissner M H and Moneta G L. Venous severity scoring: An adjunct to venous outcome assessment. J.Vasc.Surg. 2000b, 31:1307-1312

Sam R C, Silverman S H and Bradbury A W. Nerve injuries and varicose vein surgery. Eur.J.Vasc.Endovasc.Surg. 2004, 27:113-120

Sarin S, Scurr J H and Coleridge Smith P D. Stripping of the long saphenous vein in the treatment of primary varicose veins. Br.J.Surg. 1994, 81:1455-1458

Sarin S, Scurr J H and Coleridge Smith P D. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. Br.J.Surg. 1992, 79:889-893

Schultz-Ehrenburg U, Reich-Schupke S, Robak-Pawelczyk B, Rudolph T, Moll C, Weindorf N, Hirche H, Altmeyer P and Stücker M. Prospective epidemiological study on the beginning of varicose veins Bochum Study I-IV. Phlebologie -Stuttgart- 2009, Phlebologie 01/2009:17-25

Schuren J, Vos A and Allen J O. Venous leg ulcer patients with low ABPIs: how much pressure is safe and tolerable? EWMA Journal 2010, 29-34

Scott T E, LaMorte W W, Gorin D R and Menzoian J O. Risk factors for chronic venous insufficiency: a dual case-control study. J.Vasc.Surg. 1995, 22:622-628

Segiet O A, Brzozowa-Zasada M, Piecuch A, Dudek D, Reichman-Warmusz E and Wojnicz R. Biomolecular mechanisms in varicose veins development. Ann.Vasc.Surg. 2015, 29:377-384

Seldinger S I. Catheter replacement of the needle in percutaneous arteriography (a new technique). .1953, 39:368-376

- Sell H, Vikatmaa P, Alback A, Lepantalo M, Malmivaara A, Mahmoud O and Venermo M. Compression therapy versus surgery in the treatment of patients with varicose veins: A RCT. *Eur.J.Vasc.Endovasc.Surg.* 2014, 47:670-677
- Serra R, Ielapi N, Bevacqua E, Rizzuto A, De Caridi G, Massara M, Casella F, Di Mizio G and de Franciscis S. Haemorrhage from varicose veins and varicose ulceration: A systematic review. *Int.Wound.J.* 2018, 15:829-833
- Serra R, Gallelli L, Perri P, De Francesco E M, Rigracciolo D C, Mastroberto P, Maggiolini M and de Franciscis S. Estrogen Receptors and Chronic Venous Disease. *Eur.J.Vasc.Endovasc.Surg.* 2016, 52:114-118
- Shadid N, Ceulen R, Nelemans P, Dirksen C, Veraart J, Schurink G W, van Neer P, vd Kley J, de Haan E and Sommer A. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. *Br.J.Surg.* 2012, 99:1062-1070
- Shingler S, Robertson L, Boghossian S and Stewart M. Compression stockings for the initial treatment of varicose veins in patients without venous ulceration. *Cochrane Database Syst.Rev.* 2013, (12):CD008819. doi:CD008819
- Sisto T, Reunanen A, Laurikka J, Impivaara O, Heliovaara M, Knekt P and Aromaa A. Prevalence and risk factors of varicose veins in lower extremities: mini-Finland health survey. *Eur.J.Surg.* 1995, 161:405-414
- Skeik N, Kalsi H, Wysokinski W E, Heaser T V and Wennberg P W. Predicting superficial venous incompetence with strain gauge plethysmography. *Phlebology* 2012, 27:135-140
- Skott O and Carter A M. Relaxin is a vasodilator hormone. *Am.J.Physiol.Regul.Integr.Comp.Physiol.* 2002, 283:347
- Somjen G M, Ziegenbein R, Johnston A H and Royle J P. Anatomical examination of leg telangiectases with duplex scanning. *J.Dermatol.Surg.Oncol.* 1993, 19:940-945
- Stanhope J M. Varicose veins in a population of lowland New Guinea. *Int.J.Epidemiol.* 1975, 4:221-225
- Subramonia S and Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. *Br.J.Surg.* 2010, 97:328-336
- Sun J J, Chowdhury M M, Sadat U, Hayes P D and Tang T Y. Mechanochemical Ablation for Treatment of Truncal Venous Insufficiency: A Review of the Current Literature. *J.Vasc.Interv.Radiol.* 2017, 28:1422-1431

Sundaresan S, Migden M R and Silapunt S. Stasis Dermatitis: Pathophysiology, Evaluation, and Management. *Am.J.Clin.Dermatol.* 2017, 18:383-390

Tang T Y, Kam J W and Gaunt M E. ClariVein(R) - Early results from a large single-centre series of mechanochemical endovenous ablation for varicose veins. *Phlebology* 2017, 32:6-12

Taylor J, Hicks C W and Heller J A. The hemodynamic effects of pregnancy on the lower extremity venous system. *J.Vasc.Surg.Venous Lymphat Disord.* 2018, 6:246-255

Tessari L, Cavezzi A and Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. *Dermatol.Surg.* 2001, 27:58-60

Thaler E, Huch R, Huch A and Zimmermann R. Compression stockings prophylaxis of emergent varicose veins in pregnancy: a prospective randomised controlled study. *Swiss Med.Wkly.* 2001, 131:659-662

Theivacumar N S, Dellagrammaticas D, Beale R J, Mavor A I and Gough M J. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. *Br.J.Surg.* 2007, 94:722-725

Thibault P, Bray A, Wlodarczyk J and Lewis W. Cosmetic leg veins: evaluation using duplex venous imaging. *J.Dermatol.Surg.Oncol.* 1990, 16:612-618

Thomas M L. Techniques of phlebography: a review. *Eur.J.Radiol.* 1990, 11:125-130

Thomis S, Verbrugge P, Milleret R, Verbeken E, Fourneau I and Herijgers P. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. *Eur.J.Vasc.Endovasc.Surg.* 2013, 46:378-382

Trendelenburg F. Über die Unterbindung der Vena saphena magna bei unterschenkelvaricen. *Beiträge zur klinischen Chirurgie* 1890, 7:195-210

Tretbar L L. Treatment of small bleeding varicose veins with injection sclerotherapy. Bleeding blue blebs. *Dermatol.Surg.* 1996, 22:78-80

van den Bos, R. R., Malskat W S, De Maeseneer M G, de Roos K P, Groeneweg D A, Kockaert M A, Neumann H A and Nijsten T. Randomized clinical trial of endovenous laser ablation versus steam ablation (LAST trial) for great saphenous varicose veins. *Br.J.Surg.* 2014, 101:1077-1083

van den Bremer J and Moll F L. Historical overview of varicose vein surgery. *Ann.Vasc.Surg.* 2010, 24:426-432

van der Velden, S. K., Biemans A A, De Maeseneer M G, Kockaert M A, Cuypers P W, Hollestein L M, Neumann H A, Nijsten T and van den Bos, R. R. 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. *Br.J.Surg.* 2015a, 102:1184-1194
- van der Velden, S. K., Biemans A A, De Maeseneer M G, Kockaert M A, Cuypers P W, Hollestein L M, Neumann H A, Nijsten T and van den Bos, R. R. 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. *Br.J.Surg.* 2015b, 102:1184-1194
- van Eekeren R R, Boersma D, Holewijn S, Werson D A, de Vries J P and Reijnen M M. Mechanochemical endovenous ablation for the treatment of great saphenous vein insufficiency. *J.Vasc.Surg.Venous Lymphat Disord.* 2014, 2:282-288
- van Eekeren R R, Boersma D, Elias S, Holewijn S, Werson D A, de Vries J P and Reijnen M M. Endovenous mechanochemical ablation of great saphenous vein incompetence using the ClariVein device: a safety study. *J.Endovasc.Ther.* 2011, 18:328-334
- van Rij A M, Chai J, Hill G B and Christie R A. Incidence of deep vein thrombosis after varicose vein surgery. *Br.J.Surg.* 2004, 91:1582-1585
- Vasquez M A, Rabe E, McLafferty R B, Shortell C K, Marston W A, Gillespie D, Meissner M H, Rutherford R B and American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J.Vasc.Surg.* 2010, 52:1387-1396
- Vos C G, Unlu C, Bosma J, van Vlijmen C J, de Nie A J and Schreve M A. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:880-896
- Vuylsteke M E, Klitfod L and Mansilha A. Endovenous ablation. *Int.Angiol.* 2019, 38:22-38
- Wallace T, El-Sheikha J, Nandhra S, Leung C, Mohamed A, Harwood A, Smith G, Carradice D and Chetter I. Long-term outcomes of endovenous laser ablation and conventional surgery for great saphenous varicose veins. *Br.J.Surg.* 2018a, 105:1759-1767
- Wallace T, El-Sheikha J, Nandhra S, Leung C, Mohamed A, Harwood A, Smith G, Carradice D and Chetter I. Long-term outcomes of endovenous laser ablation and conventional surgery for great saphenous varicose veins. *Br.J.Surg.* 2018b, 105:1759-1767

Ward A, Abisi S and Braithwaite B D. An online patient completed Aberdeen Varicose Vein Questionnaire can help to guide primary care referrals. *Eur.J.Vasc.Endovasc.Surg.* 2013, 45:178-182

Weddell J M. Varicose veins pilot survey, 1966. *Br.J.Prev.Soc.Med.* 1969, 23:179-186

Weiss R A and Weiss M A. Doppler ultrasound findings in reticular veins of the thigh subdermic lateral venous system and implications for sclerotherapy. *J.Dermatol.Surg.Oncol.* 1993, 19:947-951

Weller C D, Team V, Ivory J D, Crawford K and Gethin G. ABPI reporting and compression recommendations in global clinical practice guidelines on venous leg ulcer management: A scoping review. *Int.Wound.J.* 2019, 16:406-419

Whiteley M S. High intensity focused ultrasound (HIFU) for the treatment of varicose veins and venous leg ulcers - a new non-invasive procedure and a potentially disruptive technology. *Curr.Med.Res.Opin.* 2019, 1-4

Whiteley M S. Glue, steam and Clarivein--Best practice techniques and evidence. *Phlebology* 2015, 30:24-28

Whitney R J. The measurement of volume changes in human limbs. *J.Physiol.* 1953, 121:1-27

Winterborn R J, Foy C and Earnshaw J J. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *J.Vasc.Surg.* 2004, 40:634-639

Witte M E, Holewijn S, van Eekeren R R, de Vries J P, Zeebregts C J and Reijnen M M. Midterm Outcome of Mechanochemical Endovenous Ablation for the Treatment of Great Saphenous Vein Insufficiency. *J.Endovasc.Ther.* 2017, 24:149-155

Witte M E, Zeebregts C J, de Borst G J, Reijnen, M. M. P. J. and Boersma D. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review. *Phlebology* 2017, 32:649-657

Wittens C, Davies A H, Baekgaard N, Broholm R, Cavezzi A, Chastanet S, de Wolf M, Eggen C, Giannoukas A, Gohel M, Kakkos S, Lawson J, Noppeney T, Onida S, Pittaluga P, Thomis S, Toonder I, Vuylsteke M, Esvs Guidelines C, Kolh P, de Borst G J, Chakfe N, Debus S, Hinchliffe R, Koncar I, Lindholt J, de Ceniga M V, Vermassen F, Verzini F, Document R, De Maeseneer M G, Blomgren L, Hartung O, Kalodiki E, Kortzen E, Lugli M, Naylor R, Nicolini P and Rosales A. Editor's Choice - Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur.J.Vasc.Endovasc.Surg.* 2015, 49:678-737

- Wollmann J C. The history of sclerosing foams. *Dermatol.Surg.* 2004, 30:694-703; discussion 703
- Wood J J, Chant H, Laugharne M, Chant T and Mitchell D C. A prospective study of cutaneous nerve injury following long saphenous vein surgery. *Eur.J.Vasc.Endovasc.Surg.* 2005, 30:654-658
- Wozniak W, Mlosek R K and Ciostek P. Complications and Failure of Endovenous Laser Ablation and Radiofrequency Ablation Procedures in Patients With Lower Extremity Varicose Veins in a 5-Year Follow-Up. *Vasc.Endovascular Surg.* 2016, 50:475-483
- Yamamoto T and Sakata M. Influence of fibers and wavelengths on the mechanism of action of endovenous laser ablation. *J.Vasc.Surg.Venous Lymphat Disord.* 2014, 2:61-69
- Yasim A, Eroglu E, Bozoglan O, Mese B, Acipayam M and Kara H. A new non-tumescent endovenous ablation method for varicose vein treatment: Early results of N-butyl cyanoacrylate (VariClose(R)). *Phlebology* 2017, 32:194-199
- Zernovicky. Fast progressive devastating granulomatic reaction after VenaSeal procedure. 2018 XVIII UIP world congress 4.-8.2.2018 Melbourne, Australia
- Zikorus A W and Mirizzi M S. Evaluation of setpoint temperature and pullback speed on vein adventitial temperature during endovenous radiofrequency energy delivery in an in-vitro model. *Vasc.Endovascular Surg.* 2004, 38:167-174
- Zollmann P, Zollmann C, Zollmann P, Veltman J, Kerzig D, Doerler M and Stucker M. Determining the origin of superficial venous reflux in the groin with duplex ultrasound and implications for varicose vein surgery. *J.Vasc.Surg.Venous Lymphat Disord.* 2017, 5:82-86

