Elimination of axial venous reflux

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ACADEMIC DISSERTATION

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# Abbreviations

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<tr>
<td>AVP</td>
<td>ambulatory venous pressure</td>
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<td>CDT</td>
<td>catheter-directed thrombolysis</td>
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<td>CEAP</td>
<td>clinical, etiological, anatomical, pathophysiological</td>
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<td>CVD</td>
<td>chronic venous disease</td>
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<td>CVI</td>
<td>chronic venous insufficiency</td>
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<td>DVI</td>
<td>deep venous incompetence</td>
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<td>DVT</td>
<td>deep venous thrombosis</td>
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<td>EVLT</td>
<td>endovenous laser therapy</td>
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<td>GSS</td>
<td>general surgical service</td>
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<td>GSV</td>
<td>great saphenous vein (previously LSV=long saphenous vein)</td>
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<td>HHD</td>
<td>hand-held doppler</td>
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<td>IPV</td>
<td>incompetent perforating vein</td>
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<td>PE</td>
<td>pulmonary embolism</td>
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<td>PTS</td>
<td>post-thrombotic syndrome</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>REVAS</td>
<td>recurrent varices after surgery</td>
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<td>RFA</td>
<td>radiofrequency ablation</td>
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<td>SFJ</td>
<td>sapheno-femoral junction</td>
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<td>SSV</td>
<td>small saphenous vein (previously short saphenous vein)</td>
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<td>UGFS</td>
<td>ultrasound-guided foam sclerotherapy</td>
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<td>VCSS</td>
<td>venous clinical severity score</td>
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<td>VDS</td>
<td>venous disability score</td>
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<td>VSS</td>
<td>vascular surgical service</td>
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List of original publications

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:

I

Oinonen A., Sugano N., Lehtola A., Suokas N., Keränen U., Lepäntalo M.
Service comparison between vascular and general surgery in the treatment of chronic venous insufficiency with special reference to preoperative Doppler techniques.

II

Oinonen A., Lehtola A., Sugano N., Albäck A., Lepäntalo M.
Communicating Doppler-derived information in superficial venous surgery.

III

Oinonen A., Lehtola A., Taavitsainen M., Schröder T.
Starting endovenous practice: Short-term results of ultrasound-guided foam sclerotherapy for axial venous reflux. Submitted for publication.

IV

Laiho MK, Oinonen A., Sugano N., Harjola VP, Lehtola AL, Roth WD, Keto PE, Lepäntalo M.

V

Lehtola A.*, Oinonen A.*, Sugano N., Albäck A., Lepäntalo M.
*equal contributions

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Abstract

**Introduction:** Chronic venous disease is a common medical condition. Its central feature is venous reflux, which may be primary, congenital, or result from an earlier episode of deep venous thrombosis. Reflux causes ambulatory venous hypertension and may result in a variety of symptoms, such as varicose veins, venous edema and ulceration. The most accurate method to evaluate reflux is duplex ultrasound, which is also the basis for the uniform classification system, CEAP (clinical, etiological, anatomical, pathophysiological). Treatments of venous reflux and of deep venous thrombosis are evolving. New duplex-based endovascular techniques are increasingly replacing traditional surgery in the elimination of reflux, and active thrombus removal aims to decrease the most severe chronic complication of deep venous thrombosis, the post-thrombotic syndrome.

**Aims of the study:** The aims were to evaluate the outcome of superficial venous surgery performed in different institutions with or without preoperative duplex evaluation and venous marking with hand-held doppler, to assess short-term outcome of ultrasound-guided foam sclerotherapy in patients with axial superficial venous incompetence, to compare reflux patterns after catheter-directed and systemic thrombolysis of deep iliofemoral venous thrombosis, and to evaluate the long-term outcome of deep venous reconstructions for severe chronic venous insufficiency.

**Patients and methods:** The study consists of five separate retrospective projects, which include a cross-sectional follow-up evaluation with duplex ultrasound:

1. Two groups of patients had undergone superficial venous surgery 2 to 5 years earlier either in vascular surgical service (VSS, 28 patients, 33 limbs) according to preoperative duplex examination and venous marking, or in general surgical service (GSS, 27 patients, 35 limbs) according to clinical evaluation.

2. A total of 78 patients with superficial venous incompetence had undergone a duplex or doppler examination and then superficial venous surgery 2 years earlier either with the surgeon performing venous marking with doppler just before the operation (39 patients, 51 limbs) or with the surgeon performing the operation according to a written plan and without venous marking (39 patients, 51 limbs).

3. The study included 112 patients who had undergone ultrasound-guided foam sclerotherapy for axial venous reflux 5.5 to 16.5 months before.

4. A total of 32 patients had suffered from deep iliofemoral venous thrombosis and received either catheter-directed or systemic thrombolysis 2 to 3 years earlier.

5. The study comprised 38 patients who had undergone different deep venous reconstructions 2 to 7 years earlier for severe primary or secondary (post-thrombotic) chronic venous insufficiency.

**Results:**

1. The proportion of recurrent or residual venous reflux in each group was about 40%. Limbs surgically treated in VSS had less axial reflux at sapheno-femoral or thigh level (4/33 vs 14/35, p=0.009).

2. Elimination of preoperatively known reflux succeeded better in the marked than in the non-marked group: The percentage of intact refluxing veins at the postoperative
ABSTRACT

evaluation was 2% vs 18% (1 of 51 vs 9 of 51, p=0.008). Although the differences were not statistically significant, residual or recurrent reflux in preoperatively identified reflux sites at the sapheno-femoral junction, in the great saphenous vein (GSV), in main branches of the GSV, or in the small saphenous vein tended to be more frequent in patients operated on without preoperative marking (5 vs 12 limbs, p=0.063).

3. The immediate occlusion rate after a single session was 90%. After the follow-up, the treated vein was fibrosed or occluded in 62%, patent with antegrade flow in 13%, partially occluded with reflux ≤1s in 11%, and patent with reflux >1s in 15%. In primary and recurrent veins the result was similar. Of all patients, 93% were satisfied with the treatment.

4. Patients treated with catheter-directed thrombolysis tended to have better clinical outcome: 56% vs 19% had no signs of venous disease or only had venular changes. They had significantly less deep and superficial venous reflux (44% vs 81%, p=0.03; 25% vs 63%, p=0.03) and a higher proportion of preserved valvular competence (44% vs 13%, p=0.049).

5. The overall cumulative clinical success rate at 4 years was 23%, in patients with primary or congenital disease it was 44%, and in secondary disease 17%. Freedom from ulceration at 4 years was 54%. Valvuloplasties were the most durable techniques with a cumulative 4-year durability rate of 55%. The durability rate for transpositions was 43%, and for transplantations 16%.

Conclusions:

Preoperative examination with duplex ultrasound and marking of reflux sites with doppler before the operation by the surgeon himself seem to improve the outcome of superficial venous surgery. Ultrasound-guided foam sclerotherapy is effective in elimination of venous reflux in selected cases in short-term follow-up. The patient satisfaction with this treatment is high.

Catheter-directed thrombolysis for deep iliofemoral venous thrombosis reduces later reflux and most probably also the development of post-thrombotic syndrome. The outcome of deep venous reconstructions, especially for post-thrombotic deep venous incompetence, is poor. Thus, prevention of valvular damage by active treatment of deep venous thrombosis is important.
Introduction

Chronic venous disease (CVD), including uncomplicated varicose veins and chronic venous insufficiency (CVI), is one of the most common medical conditions in the Western world. In recent studies, the prevalence of varicose veins among adults is 12 to 46%, and of CVI 4 to 14% (Rabe et al. 2008). The spectrum of symptoms and signs of CVD ranges from minor cosmetic problems to venous ulceration, which results in considerable morbidity and increased medical costs (Herber et al. 2007, Olin et al. 1999).

The mean incidence of newly diagnosed acute deep venous thrombosis (DVT) among the general population is 5 to 6 per 10 000 persons per year, and is strongly related to age (Fowkes et al. 2003). The most important late complication of DVT is the post-thrombotic syndrome (PTS), which consists of pain, edema, and varying degrees of skin changes including ulcer. The incidence of the severe manifestations of PTS after DVT is 2 to 10% (Lees et al. 2006), whereas some post-thrombotic symptoms may occur in up to 80% of the patients (Ziegler et al. 2001).

The central feature of CVD is venous reflux in the superficial, deep, or perforating veins, or in any combination of these (Bergan et al. 2006). In primary CVD, reflux is most likely due to weakening of the superficial vein wall and the subsequent venous dilation results in valvular incompetence (Meissner et al. 2007a). Secondary CVD usually results from an episode of acute DVT and most commonly involves a combination of reflux and obstruction in superficial and deep veins (Johnson et al. 1995). Regardless of the underlying etiology, the final pathway leading to symptoms is ambulatory venous hypertension.

The diagnosis of venous reflux has undergone a major change over the years. Initially, the only diagnostic tools were inspection and various clinical tests (Arfvidsson et al. 2004). Thereafter, hand-held doppler examination became a part of the office-phase diagnostics, but proved inaccurate in planning treatment (Kistner et al. 2001, Rautio et al. 2002a). The venous pressure studies and venography are complementary tests and provide additional information before surgical interventions. The most useful test for the evaluation of valvular incompetence as well as of obstruction is duplex ultrasound scanning, which allows a direct visualization of the venous anatomy and flow. According to current opinion, duplex examination should precede every invasive treatment of CVD (Meissner et al. 2007a). Duplex is also the basis for CEAP classification, which aims to standardize the reporting and treatment, as well as to allow uniform diagnosis and grading (Porter et al. 1995).

Modern surgery for varicose veins began in the late 19th century, when Trendelenburg described the ligation of the great saphenous vein (GSV) in the upper thigh (Trendelenburg 1891). Later, Keller and Mayo reported intraluminal stripping as a surgical procedure (Keller 1905, Mayo 1906). Because surgery caused considerable morbidity, liquid sclerotherapy replaced it as the treatment of choice (McPheters 1927, Dixon 1930). High recurrence rates, nearly 60% at 5 years (Waugh 1941), eventually inspired interest in developing new surgical techniques (Myers 1957). The high incidence of paresthesia and pain associated with routine stripping of the GSV from ankle to groin (Cox et al. 1974, Munn et al. 1981) led to technique modification. Later, retrograde groi-
to-knee stripping of the GSV became the standard operation (Dwerryhouse et al. 1999). Although this procedure includes risk for nerve injury as well, its occurrence is far less frequent (Sam et al. 2004a). However, recurrence of varicose veins after surgery remains a problem (Winterborn et al. 2004). Re-operations can be difficult to perform due to the usual tortuosity and dilation of the thin-walled vessels at the scarred sapheno-femoral junction.

The invasiveness of surgery and high recurrence rate, as well as risks related to re-operations, have led to development of new treatments. Currently, ultrasound-based endovascular techniques are increasingly replacing traditional surgery in the treatment of superficial venous incompetence. However, the long-term outcomes of ultrasound-guided foam sclerotherapy, radiofrequency ablation, and endovenous laser therapy remain unknown.

The main purpose of the treatment of CVD is the elimination of the axial superficial venous reflux playing a major role in development of skin lesions (Tassiopoulos et al. 2000). Currently, the diagnostic methods give a precise picture of the venous hemodynamics and enable adequate therapy. The main goal of this thesis project was to study the accuracy of preoperative diagnostics in guiding ablative venous surgery to eliminate axial venous reflux. In addition, this project evaluates the chances to preserve venous valve function after DVT with an efficient thrombolytic therapy, as well as the outcomes of deep venous reconstructions for severe CVD, and of ultrasound-guided foam sclerotherapy for superficial venous incompetence.
Review of the literature

1 Anatomy of the venous system

The venous system is much more complicated than the arterial system, and anatomic variations are common (Cavezzi et al. 2006). The venous network of the lower extremity consists of the superficial veins, which course in the subcutaneous fat outside the deep fascia and drain the skin and subcutaneous tissue; the deep veins, which lie beneath the fascia and drain the calf and thigh muscles; and the perforating veins that penetrate the deep fascia and connect the superficial to the deep veins. All these veins contain bicuspid valves that normally allow unidirectional flow toward the heart. In perforating veins the blood flows from superficial to deep veins. The valves consist of endothelium and a connective tissue skeleton, and although thin, are mechanically strong structures (Ackroyd et al. 1985, Mozes et al. 2001). An International Interdisciplinary Consensus Committee on Venous Anatomical Terminology has updated the nomenclature of the lower extremity veins (Caggiati et al. 2002, 2005).

1.1 Superficial veins

The main veins of the medial superficial system are the great saphenous vein and the anterior and posterior accessory great saphenous veins (Fig 1). The GSV is duplicated in the thigh in 1 to 8% of the limbs (Cavezzi et al. 2006, Mozes et al. 2001), and the anatomy of the tributaries varies (Cavezzi et al. 2006). Corrales et al. (2002) have reported much higher incidence of GSV duplication: 49%. In the calf, the GSV and the saphenous nerve are in close proximity.

The main posterior superficial vein of the leg is the small saphenous vein (SSV) (Fig 1). The level of the sapheno-popliteal junction is variable, and usually the SSV also has a thigh extension which can terminate in the upper thigh in various ways. Sometimes a cranial extension of the SSV communicates with the GSV via the posterior circumflex vein (the vein of Giacomini) without connection to deep veins in the popliteal fossa (Cavezzi et al. 2006). In the foot and lower calf, the sural nerve courses close to the SSV.

1.2 Deep veins

The deep veins accompany the corresponding arteries and are quite often duplicated below the knee (Fig 1). The deep veins of the calf (anterior, posterior tibial and peroneal veins) unite to form the popliteal vein, which becomes the femoral vein in the adductor canal. The gastrocnemius veins, which drain the gastrocnemius muscles, empty into the SSV or the popliteal vein. The femoral vein (FV) unites the deep femoral vein at about 9 cm below the inguinal ligament. The common femoral vein is the continuation of the FV after this joining point and ends at the inguinal ligament where it continues in the external iliac
REVIEW OF THE LITERATURE

Figure 1. Main superficial, perforating and deep veins of the thigh and calf (illustration by Anita Mäkelä)

Anterior view                   Posterior view

vein (Mozes et al. 2001). The external iliac vein joins the internal iliac vein to form the common iliac vein, which then drains into the inferior vena cava.

1.3 Perforating veins

Clinically the most important perforating veins are the medial calf perforators (Stuart et al. 2000) (Fig 1). The posterior tibial perforators (Cockett perforators) connect the posterior accessory GSV, and the paratibial perforators the main GSV trunk with the posterior tibial veins. The number of perforating veins, and their size and connections vary considerably. The direct perforators, which connect the superficial to deep axial veins, have a rather constant anatomic distribution; whereas the indirect perforators, which join venous sinuses of the calf muscles, are randomly distributed (Mozes et al. 2001). The major perforators have bicuspid valves, and direct the flow from the superficial to the deep veins, whereas smaller perforators are valveless, and allow bidirectional flow.
2 Physiology of the normal veins

The main function of the lower extremity venous system is to return venous blood toward the heart. An effective venous return requires a central pump, a pressure gradient, a peripheral pump, and competent venous valves. In the upright position, the gravity and hydrostatic pressure oppose the return flow. The calf muscle pump and the venous valves work to overcome these forces.

2.1 The calf muscle pump

The gastrocnemius and soleus muscles form the calf muscle pump (Fig 2). Beginning at the resting hydrostatic pressure (approximately 100 mmHg), a single muscle contraction ejects 40 to 60% of the venous volume in the calf into the popliteal vein, and a few additional contractions reduce the pressure gradually to the level of the ambulatory venous pressure (AVP, mean 22 mmHg) (Meissner et al. 2007a). In clinical practice, measurement of this end-exercise pressure evaluates the calf muscle pump function. After the contractions in the normal limb cease, some 30 seconds are required to restore the hydrostatic pressure (venous refill time) (Padberg 2001).

Figure 2. Function of the calf muscle pump and the venous valves (illustration by Anita Mäkelä)

2.2 The venous valvular function

The venous valves function to divide the blood column into segments and to prevent retrograde venous flow. After active contraction, the muscles relax, and the valves in the deep and superficial veins normally close in <0.5 seconds (van Bemmelen et al. 1989), whereas the valves within the perforating veins open, and the blood-flow follows the pressure gradient from the superficial to deep veins (Fig 2). The importance of the anatomic sites of the valves remains unclear, as does the importance of any dysfunction of a single or even several valves (Padberg 2001).
3 Pathophysiology of chronic venous disease

Chronic venous disease refers to a set of symptoms and signs caused by elevated venous pressure. According to the updated terminology CVD includes “morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care”. Further, chronic venous insufficiency is a term that more specifically refers to increased severity of the disease causing edema and skin changes associated with sustained venous hypertension (Eklof et al. 2009).

3.1 Pathophysiology of reflux and obstruction

The central feature of CVD is venous reflux, which is due to either primary, congenital, or secondary valvular incompetence in superficial, deep, or perforating veins, or in combinations of these. Primary valvular incompetence is present in 70 to 80%, it is congenital in 1 to 3%, and is secondary in 18 to 25% (Bergan et al. 2006). Reflux is generally a result of gravity or of increased intra-abdominal pressure (Belcaro et al. 1995). Obstruction most commonly results from incomplete recanalization of a deep vein after acute DVT.

3.1.1 Primary chronic venous disease

The cause of primary valvular incompetence remains unknown. Recent studies suggest that structural changes that cause weakening of the superficial vein wall precede the development of reflux (Meissner et al. 2007b). Thus, superficial valvular incompetence would be secondary to the dilation of the vein wall that causes enlargement of the valve ring. After muscle contraction, the incomplete closure of the valve cusps causes retrograde flow and rapid refillment of the vein. Any superficial vein may become incompetent (Labropoulos et al. 1997), and primary superficial venous incompetence may coexist with deep venous reflux (Labropoulos et al. 2000). In that study, the prevalence of deep venous incompetence in patients with primary superficial venous reflux was 22%, but this reflux was segmental and of short duration.

In patients with primary uncomplicated varicose veins, superficial venous reflux alone in the great saphenous vein is the most common finding, whereas patients with ulcer may have more complicated reflux patterns (Myers et al. 1995). However, in a review by Tassiopoulos et al. (2000), the rate of superficial reflux alone among all ulcer patients was high, 45%, and the overall involvement of superficial veins in these patients was 88%.

In primary deep venous incompetence, one or several venous valves in the deep veins are floppy and thus unable to prevent retrograde flow after calf muscle contraction (Kistner et al. 1995). The cause of this structural weakness of the valve is unknown. Deep venous reflux alone is uncommon but may be more prevalent in men than in women (Allan et al. 2000).
The perforating veins may become primarily incompetent, similar to the process in superficial veins. The hemodynamic role of incompetent perforating veins (IPVs) remains controversial, although it is clear that, with the clinical severity of CVD, the number of IPVs, and the diameter of both competent and incompetent perforating veins increase (Labropoulos et al. 1996a, 1999). Perforating vein insufficiency most commonly coexists with superficial venous incompetence (Stuart et al. 2001).

3.1.2 Congenital chronic venous disease

Congenital venous abnormalities are present at birth, but may not become symptomatic until later. The most common syndrome associated with venous malformations is Klippel-Trenaunay syndrome (Rachel et al. 2001).

Other congenital abnormalities that may cause reflux in superficial or deep veins include persistence of embryonic veins, valvular agenesis or aplasia, venous aneurysms, and arteriovenous malformations and fistulas (Rachel et al. 2001, Slagsvold 2004). Congenital membranous obstruction of the inferior vena cava (IVC) may cause similar symptoms to those in deep venous incompetence (Slagsvold 2004). However, controversy exists as to whether this condition is a developmental abnormality, or rather the end result of organization of a thrombus in the hepatic portion of the IVC (Kew et al. 2006).

3.1.3 Secondary chronic venous disease

While the underlying cause of primary CVD is unknown, secondary CVD results from an antecedent event, usually an acute DVT. When the history of previous DVT is clear, the clinical manifestations of secondary CVD are commonly referred to as the post-thrombotic syndrome. Other rare causes of secondary CVD include venous trauma, surgical mishap, and leiomyomas and leiomyosarcomas (Burnand 2001).

Venous thrombosis is a result of at least one of the three factors known as Virchow’s triad: hypercoagulability, venous stasis, and endothelial damage. The formation of a thrombus in the vein triggers an inflammatory response leading to endogenous fibrinolysis, which results in recanalization and resolution of the mass (Meissner et al. 2001, 2007c). If the local conditions favor thrombosis, the thrombus may also extend to adjacent venous segments (Meissner et al. 2001, 2007c). Occasionally, fragments of thrombus break off, and are carried through the bloodstream until they lodge in the pulmonary arteries (Wheeler et al. 2001). Pulmonary embolism (PE) is the most important acute complication of DVT, and the third leading cause of death from cardiovascular disease (Giuntini et al. 1995).

The most significant recanalization of the thrombus occurs within the first 3 months after acute DVT and competes with recurrent thrombotic events (Meissner et al. 2007c). The long-term outcome of DVT is often unpredictable and unrelated to the original extent of the thrombus (Meissner et al. 1998, Prandoni et al. 1996). However, post-thrombotic morbidity is more severe in patients with iliofemoral DVT than in patients with infrainguinal DVT (Comerota et al. 2007a). Thrombus resolution is a complex process and
often causes some degree of vein wall fibrosis, which may then lead to vein valve dysfunction and valvular incompetence (Meissner et al. 2001). Reflux usually develops during the first 6 to 12 months after the acute episode and may be transient (Caps et al. 1995). The symptoms related to PTS most commonly occur within 2 years (Brandjes et al. 1997, Prandoni et al. 1996).Incomplete recanalization results in variable out-flow obstruction. The clinical severity of PTS depends upon the extent of reflux and obstruction as well as upon recurrent thrombotic events. Popliteal vein reflux, recurrent ipsilateral DVT, and a combination of reflux and obstruction all have the highest likelihood for development of severe post-thrombotic syndrome (Brittenden et al. 1998, Johnson et al. 1995, Prandoni 2001).

Post-thrombotic deep venous incompetence may lead to secondary perforating and superficial venous incompetence. In the presence of out-flow obstruction, the superficial trunk veins may serve for collateral venous return. During muscle contraction, the blood flows from deep to superficial veins through any associated incompetent perforating veins, resulting in a rapid return to high resting pressure (Burnand 2001).

Chronic obstruction in superficial veins is of little clinical importance, because the venous return is primarily a function of the deep veins. Acute obstruction—or superficial venous thrombophlebitis (SVT)—may, however, cause significant morbidity. The thrombosis may even extend to deep veins and cause pulmonary embolism (Verlato et al. 1999). The rate of progression of superficial venous thrombosis to deep veins has ranged between 9 to 31% (Lepäntalo 2004). SVT results from a trauma of the vein wall with simultaneous venous stasis. The role of a hypercoagulable state in association with SVT is unclear; SVT may occur in a normal vein, but the most common predisposing factor is the presence of varicose veins (Meissner et al. 2007c).

3.2 Pathophysiology of calf muscle pump dysfunction

Although reflux is undoubtedly the most important pathophysiologic mechanism leading to CVD, calf muscle pump function has an effect on the severity of the disease. Muscle pump dysfunction owing to obesity or leg immobility plays a significant role, especially in development of venous ulceration (Araki et al. 1994, Christopoulos et al. 1989).

3.3 Pathophysiology of varicose veins

Varicose veins are the most common clinical manifestation of CVD. They are dilated and twisted subcutaneous veins with a diameter of 3 mm or larger (Bergan et al. 2006) and are often associated with incompetent valves within the vein. In primary CVD, the vein wall dilation and subsequent valvular incompetence leads to increased venous pressure in a standing position, which results in increased vein wall tension and endothelial injury. Several molecular mechanisms mediate further wall dilation and varicose vein formation (Raffetto et al. 2008). In secondary CVD, the increased pressure in the deep veins is transmitted to the superficial system through IPVs, resulting in dilation of the superficial veins (Burnand 2001). Any superficial vein may become varicose. The tributaries usually
dilate before the main trunks, which have stronger supportive structures preventing
dilation in the early stages of the disease (Mozes et al. 2001).

3.4 Pathophysiology of chronic venous insufficiency

Skin changes in CVD become more severe with increasing ambulatory venous pressure
(Payne et al. 1996). Venous ulcers do not occur, when AVP is less than 30 mmHg,
whereas the occurrence of ulceration is 100% in patients with AVP of more than 90
mmHg (Nicolaides et al. 1993).

Several theories have tried to explain the mechanisms leading to ulceration and other
skin changes associated with venous hypertension (Pappas et al. 2001). These include
venous stasis theory, which emphasized the role of hypoxia, arteriovenous fistula and
diffusion block theories, as well as leukocyte trapping theory (Pappas et al. 2001).
According to current knowledge, venous hypertension in the capillaries causes chronic
inflammation, which leads to increased capillary permeability and dermal tissue fibrosis
(Bergan et al. 2006). Capillary leakage results in edema and reinforcement of the
inflammatory response. The extravasation of red blood cells and subsequent hemosiderin
deposition leads to hyperpigmentation and elevated levels of ferritin and ferric iron in the
affected skin. This may promote tissue damage and delay healing (Bergan et al. 2006).

The exact role of the white blood cells in the pathogenesis of CVI is somewhat
unclear, although the leukocytes seem to accumulate in the leg under conditions of high
venous pressure (Thomas et al. 1988). They mediate the inflammation by activating
cytokines (Meissner et al. 2007b). Cytokines and growth factors induce matrix
metalloproteinases (MMPs), which are molecules that degrade extracellular matrix (ECM)
(Jacob et al. 2001). Wecktroth et al. (1996) found increased MMP activities in ulcer
exudate and decreased expression of the tissue inhibitor of MMPs in keratinocytes,
findings suggesting that unrestrained MMP activity may contribute to the breakdown of
ECM, leading to ulcer formation and impaired healing.

4 Risk factors for chronic venous disease

Several epidemiologic studies have evaluated factors that increase risk for CVD.
Predisposing factors associated with varicose veins and CVI differ slightly. The
established risk factors predisposing to primary varicose veins include family history
(genetic predisposition), older age, female gender, pregnancy, obesity, and standing
gender and obesity probably do not increase the risk for CVI, whereas genetic factors, and
older age, as well as history of DVT, do. The roles of several potential risk factors, such as
smoking, diet, hypertension, physical activity, and exogenous hormone use, are still
unclear (Beebe-Dimmer et al. 2005).

Although many studies have confirmed the family aggregation of CVD, identification
of specific genes has been unsuccessful (Pistorius 2003). Varicose veins most likely result
from genetic heterogeneity as well as environmental factors. Prevalence of varicose veins and ulcers clearly increase with age (Fowkes et al. 2001). This is most likely due to gradual weakening of the calf muscle pump and the vein walls. Many studies have demonstrated higher prevalence of varicose veins among women than among men, although in some studies the occurrence of varicosities have not significantly differed between sexes, especially in the older population (Fowkes et al. 2001). The increased risk for varicose vein formation among women may be due to pregnancy (Beebe-Dimmer et al. 2005). Several physiological changes, such as increased blood volume and intra-abdominal pressure, predispose to vein wall dilation and valvular incompetence. The association between obesity and CVD remains slightly controversial, and seems to be significant in women only (Beebe-Dimmer et al. 2005, Fowkes et al. 2001). The role played by prolonged standing in one’s occupation is also under debate. Several studies have indicated that standing leads to increased risk for varicose veins, although measuring types of posture over a lifetime is difficult (Beebe-Dimmer et al. 2005, Fowkes et al. 2001).

Acute DVT increases risk for the development of the post-thrombotic syndrome. Several acquired and intrinsic factors predispose to venous thromboembolism (VTE). They include age, obesity, history of DVT, trauma, surgery, immobility, cancer, pregnancy and puerperium, and oral contraceptives and hormone replacement therapy, as well as thrombophilia (Ageno et al. 2006).

Thrombophilias include conditions associated with reduced levels of anticoagulant proteins and increased levels or functions of the coagulation factors, and they can be either inherited or acquired. Hereditary prothrombotic conditions include antithrombin deficiency, protein C and S deficiencies, activated protein C resistance and factor V Leiden mutation, prothrombin gene mutation, and increased concentrations of factors VIII, IX, and XI, and hyperhomocysteinemia (Ageno et al. 2006). The most common abnormality is factor V Leiden mutation, present in about 5% of the normal population in Europe (Koster et al. 1993). Relative risks for VTE associated with these conditions most commonly range between 0.8 and 8.1, and are the highest in patients with homozygote factor V Leiden mutation: 24-80 (Cushman 2007).

Hyperhomocysteinemia may be acquired, resulting from dietary deficiency of folate, vitamin B12, or B6, but lowering the level with vitamin supplementation does not seem to prevent recurrent thrombosis (den Heijer et al. 2007). In a meta-analysis of case-control studies, the overall relative risk for VTE in patients with hyperhomocysteinemia was 1.6 (den Heijer et al. 2005). The most important acquired thrombophilia is antiphospholipid antibody syndrome, a potentially severe condition; it causes both venous and arterial thrombosis as well as recurrent pregnancy loss (Levine et al. 2002). The prevalence of anticardiolipin antibodies and lupus anticoagulants in the general population is 1 to 5% (Anderson et al. 2003). The relative risk of VTE in this condition is not clear, but in the Physicians’ Health Study it was 5.3 (Ginsburg et al. 1992).
Table 1. CEAP classification (some data from Eklof et al. 2004)

Clinical classification
- C0: no visible or palpable signs of venous disease
- C1: teleangiectasies (dilated intradermal venules less than 1 mm in caliber) or reticular veins (dilated subdermal veins less than 3 mm in caliber)
- C2: varicose veins (diameter ≥3 mm)
- C3: venous edema
- C4a: pigmentation (brownish darkening of the skin) or eczema
- C4b: lipodermatosclerosis (localized chronic inflammation and fibrosis of the skin and subcutaneous tissue) or atrophie blanche (localized whitish and atrophic skin area surrounded by dilated capillaries and sometimes hyperpigmentation)
- C5: healed venous ulceration
- C6: active venous ulceration
- S: symptomatic
- A: asymptomatic

Etiologic classification
- Ec: congenital
- Ep: primary
- Es: secondary (post-thrombotic)
- En: no venous cause identified

Anatomic classification
- As: superficial veins
- Ap: perforating veins
- Ad: deep veins
- An: no venous location identified

Pathophysiologic classification
- Pr: reflux
- Po: obstruction
- Pr,o: reflux and obstruction
- Pn: no venous pathophysiology identifiable

5 Classification and outcome measures of chronic venous disease

5.1 CEAP classification

In 1994, the American Venous Forum created a classification system for CVD in order to standardize the reporting and treatment and to allow uniform diagnosis (Porter et al. 1995). The first revision of the CEAP classification was completed in 2004 (Eklof et al. 2004) and includes the clinical class (C), the etiology (E), the anatomical (A) distribution of reflux and obstruction, and the pathophysiology (P) of the disease (Table 1). Symptoms of CVD include ache, pain, tightness, heaviness and tension, a feeling of swelling, tiredness, restless legs, nocturnal muscle cramps, itching and skin irritation (Bradbury et al. 2001). The anatomic and pathophysiologic classifications are based on duplex ultrasound examination. Reflux and obstruction can be further localized to precise venous segments (Table 2).
Table 2. Venous segments

**Superficial veins**
- Teleangiectasies or reticular veins
- Great saphenous vein above knee
- Great saphenous vein below knee
- Small saphenous vein
- Nonsaphenous vein

**Deep veins**
- Inferior vena cava
- Common iliac vein
- Internal iliac vein
- External iliac vein
- Pelvic: gonadal, broad ligaments, other
- Common femoral vein
- Deep femoral vein
- Femoral vein
- Popliteal vein
- Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
- Muscular: gastrocnemial, soleal veins, other

**Perforating veins**
- Thigh
- Calf

### 5.2 Venous scoring systems

The American Venous Forum also developed venous severity scoring systems to assess severity of the disease and the outcome of treatment (Rutherford et al. 2000). The venous clinical severity score (VCSS) includes ten characteristics of CVD graded from 0 to 3 according to severity (Table 3). Meissner et al. (2002) have demonstrated that VCSS is reliable and correlates well with the CEAP clinical classification. The venous segmental disease score (VSDS) combines the anatomic and pathophysiologic components of CEAP and is based on imaging, primarily duplex, findings (Table 4). Finally, venous disability score (VSD) assesses the effect of the disease on the normal functions and ability to work or to carry out other usual activities (Table 5). In the original disability score developed with CEAP, disability is related to an 8-hour working day (Nicolaides 1996). In the present study, we used the older version, but paralleled other usual activities by an 8-hour working day, if the patient ordinarily did not work.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Absent = 0</th>
<th>Mild = 1</th>
<th>Moderate = 2</th>
<th>Severe = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional, not restricting activity or requiring analgesics</td>
<td>Daily, moderate activity limitation, occasional analgesics</td>
<td>Daily, severe limiting activities or requiring regular use of analgesics</td>
</tr>
<tr>
<td>Varicose veins*</td>
<td>None</td>
<td>Few, scattered: branch VV’s</td>
<td>Multiple: GS varicose veins confined to calf or thigh</td>
<td>Extensive: Thigh and calf or GS and LS distribution</td>
</tr>
<tr>
<td>Venous edema†</td>
<td>None</td>
<td>Evening ankle edema only</td>
<td>Afternoon edema, above ankle</td>
<td>Morning edema above ankle and requiring activity change, elevation</td>
</tr>
<tr>
<td>Skin pigmentation‡</td>
<td>None or focal, low intensity (tan)</td>
<td>Diffuse, but limited in area and old (brown)</td>
<td>Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)</td>
<td>Wider distribution (above lower 1/3) and recent pigmentation</td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>Mild cellulitis, limited to marginal area around ulcer</td>
<td>Moderate cellulitis, involves most of gaiter area (lower 1/3)</td>
<td>Severe cellulitis (lower 1/3 and above) or significant venous eczema</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal, circummalleolar (&lt; 5 cm)</td>
<td>Medial or lateral, less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>No. of active ulcers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Active ulceration, duration</td>
<td>None</td>
<td>&lt; 3 mo</td>
<td>&gt; 3 mo, &lt; 1 y</td>
<td>Not healed &gt; 1 y</td>
</tr>
<tr>
<td>Active ulcer, size§</td>
<td>None</td>
<td>&lt; 2 cm-diameter</td>
<td>2- to 6-cm diameter</td>
<td>&gt; 6-cm diameter</td>
</tr>
<tr>
<td>Compressive therapyII</td>
<td>Not used or not compliant</td>
<td>Intermittent use of stockings</td>
<td>Wears elastic stockings most days</td>
<td>Full compliance: stockings + elevation</td>
</tr>
</tbody>
</table>

* “Varicose” veins must be > 4-mm diameter to qualify so that differentiation [SIC] is ensured between C1 and C2 venous pathology.
† Presumes venous origin by characteristics (eg, Brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and / or other clinical evidence of venous etiology (ie, varicose veins, history of DVT). Edema must be regular finding (eg, daily occurrence). Occasional or mild edema does not qualify.
‡ Focal pigmentation over varicose veins does not qualify.
§ Largest dimension / diameter of largest ulcer.
II Sliding scale to adjust for background differences in use of compressive therapy.
GS, Greater saphenous; LS, lesser saphenous [Here, “great / small saphenous”]
Table 4. **VSDS [Venous segmental disease score]** (based on venous segmental involvement with reflux or obstruction*) (Reprinted from Journal of Vascular Surgery 31, Rutherford RB, Padberg FT, Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: An adjunct to venous outcome assessment, 1307-1312, 2000, with permission from Elsevier)

<table>
<thead>
<tr>
<th>Reflux</th>
<th>Obstruction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ Lesser saphenous [Here, small saphenous]</td>
<td>‡</td>
</tr>
<tr>
<td>1 Greater saphenous [Here, great saphenous]</td>
<td>1 Greater saphenous (only if thrombosed from groin to below knee)‡</td>
</tr>
<tr>
<td>½ Perforators, thigh</td>
<td>‡</td>
</tr>
<tr>
<td>1 Perforators, calf</td>
<td>‡</td>
</tr>
<tr>
<td>2 Calf veins, multiple (PT alone = 1)</td>
<td>1 Calf veins, multiple</td>
</tr>
<tr>
<td>2 Popliteal vein</td>
<td>2 Popliteal vein</td>
</tr>
<tr>
<td>1 Superficial femoral vein [Here, femoral vein]</td>
<td>1 Superficial femoral vein</td>
</tr>
<tr>
<td>1 Profunda femoris vein [Here, deep femoral vein]</td>
<td>1 Profunda femoris vein</td>
</tr>
<tr>
<td>1 Common femoral vein and above‡</td>
<td>2 Common femoral</td>
</tr>
<tr>
<td>10 Maximum reflux score§</td>
<td>10 Maximum obstruction score§</td>
</tr>
</tbody>
</table>

Note: Reflux means that all the valves in that segment are incompetent. Obstruction means there is total occlusion at some point in the segment or > 50% narrowing of at least half of the segment. Most segments are assigned one point, but some segments have been weighted more or less to fit with their perceived significance (eg, increasing points for common femoral or popliteal obstruction and for popliteal and multiple calf vein reflux and decreasing points for lesser saphenous or thigh perforator reflux). Points can be assigned for both obstruction and reflux in the same segment. This will be uncommon but can occur in some postthrombotic states, potentially giving secondary venous insufficiency higher severity scores than primary disease.

* As determined by appropriate venous imaging (phlebography or duplex scan). Although some segments may not be routinely studied in some laboratories (eg, profund femoris and tibial veins), points cannot be awarded on the basis of presumption, without interrogating the segments for obstruction or reflux.

† The excision, ligation, or traumatic obstruction of deep venous segments counts toward obstruction points just as much as their thrombosis.

‡ Normally there are no valves above the common femoral vein, so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision do not count in the obstruction score, but as a reduction of the reflux score.

§ Not all of the 11 segments can be involved in reflux or obstruction. Ten is the maximum score that can be assigned, and this might be achieved by complete reflux at all segmental levels.

IVC, Inferior vena cava; PT, posterior tibial.


<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>symptomatic but able to carry out usual activities* without compressive therapy</td>
</tr>
<tr>
<td>2</td>
<td>can carry out usual activities* only with compression and/or limb elevation</td>
</tr>
<tr>
<td>3</td>
<td>unable to carry out usual activities* even with compression and/or limb elevation</td>
</tr>
</tbody>
</table>

* Usual activities = patients activities before onset of disability from venous disease.
5.3 Quality of life measurements

Quality of life (QoL) describes the functional effect of an illness and of its therapy upon a patient. It has become an important outcome measure in diagnostic and treatment studies, and also in chronic venous disease. Health-related quality of life (HRQoL) measurements fall into two categories: generic and disease-specific. Generic instruments assess HRQoL in general and allow comparisons across populations of patients with different diseases, whereas disease-specific instruments assess the effect of a particular disease and are likely to be sensitive to change (Patrick et al. 1989).

Van Korlaar et al. (2003) have reviewed the literature regarding the impact of CVD on QoL. Most studies were questionnaire-surveys, and formal evaluation of reliability and validity of some questionnaires were lacking. The most frequently used generic QoL instrument was the Short Form 36 (SF-36), which is the most widely evaluated measure of generic QoL instruments (Garrett et al. 2002) (Table 6). Results indicated that patients with CVD have reduced QoL, mostly with regard to pain, physical functioning, and mobility. They also suffer from negative emotional reactions and social isolation (van Korlaar et al. 2003). Using SF-36 and venous disease-specific QoL (VEINES-QOL) and symptom-severity (VEINES-Sym) QoL questionnaires, Kahn et al. (2004) showed that the impact of CVD on HRQoL increases with increasing clinical classification.

5.3.1 15D

The Finnish 15D is a generic, standardized, self-administered measure of HRQoL (Sintonen 2001). It includes the following 15 dimensions: breathing, mental function, speech, vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is divided into five levels. The maximum score is one (no problems in any dimension), and the minimum zero (being dead) (Appendix I). The 15D is feasible and validated, and its discriminatory power is better than or comparable to those of the NHP, EQ-5D, and SF-20 (Räsänen et al. 2005, Sintonen 2001).

5.3.2 Aberdeen questionnaire

The Aberdeen questionnaire, designed in 1993, specifically assesses HRQoL in patients with varicose veins (Garratt et al. 1993). It consists of 14 questions relating to pain, ankle swelling, use of support stockings, skin changes, interference with social and domestic activities, and the cosmetic aspects. In the first section, the patients can sketch the distribution of their varicosities. The scoring is from zero to 100 (Appendix II). Smith et al. in 1999 aimed to validate the Aberdeen questionnaire as a measure of health outcome and concluded that the questionnaire is valid for patients with varicose veins. They also showed that these patients have reduced QoL compared with that of the general population, and that an operation improves this discrepancy.
### Table 6. Commonly used generic and disease-specific quality of life instruments in venous disease

<table>
<thead>
<tr>
<th>Generic QoL instruments</th>
<th>Disease-specific QoL instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Form 36 (SF-36)</td>
<td>The Freiburger Questionnaire of QoL in venous diseases (FLQA)</td>
</tr>
<tr>
<td>Short Form 20 (SF-20)</td>
<td>Health questionnaire for venous disease</td>
</tr>
<tr>
<td>Short Form 12 (SF-12)</td>
<td>The Tübingen questionnaire for chronic venous insufficiency (TLC-CVI)</td>
</tr>
<tr>
<td>Frenchay Activities Index (FAI)</td>
<td>Venous Insufficiency Epidemiologic and Economic Study Questionnaire (VEINES-QOL)</td>
</tr>
<tr>
<td>Nottingham Health Profile (NHP)</td>
<td>Chronic Lower Limb Venous Insufficiency Questionnaire (CIVIQ)</td>
</tr>
<tr>
<td>Symptom Rating Test (SRT)</td>
<td>Health questionnaire for leg ulcers</td>
</tr>
<tr>
<td>McGill Short Form Pain Questionnaire (SF-MPQ)</td>
<td>Self-report QOL questionnaire for patients with venous leg ulcers</td>
</tr>
<tr>
<td>EuroQoL (EQ-5D)</td>
<td>Charing Cross venous ulcer questionnaire</td>
</tr>
<tr>
<td>15D</td>
<td>Clinical varicose veins questionnaire (Aberdeen questionnaire)</td>
</tr>
</tbody>
</table>

### 6 Diagnosis of venous reflux

#### 6.1 Clinical evaluation

The patient history may be misleading due to the fact that the symptoms of venous disease are unspecific. The Edinburgh Vein Study demonstrated that lower limb symptoms are common in the general population and have a weak correlation with CVD presence and severity, and with the pattern of venous reflux (Bradbury et al. 1999, 2000).

The patient should be examined standing, preferably on a platform with handrails, in a warm room. The clinical examination begins with inspection of the legs. Although physical findings are characteristic, they provide little information about the presence or location of valvular incompetence or obstruction. Clinical tests such as Trendelenburg and Perthes’ tests are also inaccurate methods to evaluate the underlying pathophysiology of venous disease (Kistner et al. 2001, McIrvine et al. 1984). Neither is the etiology of an ulcer always evident. Although most lower limb ulcers are venous in origin, ischemic and mixed arterial and venous ulcers are also common (Negus et al. 2005). The differential diagnosis includes diabetic and traumatic ulcers as well as vascular malformations, rheumatoid disease, vasculitis, steroids, edema, infection, and malignancy (Negus et al. 2005). Ulcer assessment should always include pulse palpation and measurement of ankle brachial index (ABI). Because many other diseases may cause the same symptoms as CVD, it is mandatory also to perform a rough general physical examination.
6.2 Doppler techniques

Modern non-invasive diagnostics of venous disease rely on various devices, of which function is based on the doppler effect. These include continuous wave doppler (CWD) ultrasound or hand-held doppler (HDD) as well as duplex ultrasound, which combines pulsed wave doppler information with B-mode image.

6.2.1 Hand-held doppler

Hand-held doppler examination is a rather simple and rapid method to evaluate venous disease proving to be superior to clinical assessment alone in identifying the sites of superficial venous incompetence (McIrvin e et al. 1984, Mitchell et al. 1987). During recent decades, it therefore became part of the routine venous examination.

In the HDD examination, the leg should be relaxed. In order to facilitate the passage of ultrasound, coupling gel is applied to the skin, and the probe is placed above a vein. Since the depth of penetration of sound waves is inversely related to frequency of the transmitted ultrasound, low frequencies (5MHz) are suitable for studying deep veins, whereas superficial veins can be more clearly visualized with higher frequencies (10MHz). Valvular incompetence is detected by demonstrating flow reversal. Reflux can be provoked in a standing position by the release of manual calf compression, or by the Valsalva maneuver, which increases intra-abdominal pressure and induces reverse flow in an insufficient vein segment or junction (Mattos et al. 2001). The threshold for pathological reflux time is usually set at 0.5 seconds (Labropoulos et al. 2003, Sarin et al. 1994a), although some authors have the limit of significant reflux at 1.0 second (Campbell et al. 2005, Daher et al. 2001, Rautio et al. 2002a).

HDD examination is easy to perform and inexpensive and requires minimal equipment. In some studies, it has been relatively accurate in evaluation of primary great saphenous vein reflux with sensitivity up to 95% (Darke et al. 1997). However, in another study, the sensitivity was only 58% (Rautio et al. 2002a). The value of HHD examination is limited for the popliteal fossa because of the inability of CWD to differentiate among popliteal, small saphenous, and gastrocnemius veins (Mattos et al. 2001). Similarly, evaluation of sapheno-popliteal junction incompetence with HDD is inaccurate. The sensitivities range from 23% (Rautio et al. 2002a) to 90% (Darke et al. 1997). Some authors have suggested that HDD could serve as a screening test in patients with primary uncomplicated varicose veins (Campbell et al. 1997, 2005), while others claim that “preoperative duplex imaging is required before all operations for primary varicose veins” (Mercer et al. 1998).

6.2.2 Duplex ultrasound

Duplex ultrasound combines pulsed doppler information and conventional B-mode imaging information to allow visualization of the vessels and flow. Doppler signals are converted into colors that are overlaid on the image of the blood vessel and that represent
the speed and direction of blood flow through the vessel. This is sometimes called triplex modality. Blue color usually represents flow toward the heart and red toward the periphery, and color intensity represents velocity. The ability to visualize the veins ensures accurate placement of the probe and differentiation of individual veins and arteries. Thus, duplex scanning has overcome most of the limitations of CWD (Mattos et al. 2001).

Techniques for evaluating valvular incompetence with duplex scanning are essentially quite similar to those employed with CWD. A high-frequency linear array transducer of 7.5-13MHz is appropriate for most lower limbs (Coleridge-Smith et al. 2006). Van Bemmelen et al. described in 1989 a preferred method to perform the examination. With the patient standing, the probe is positioned over the appropriate vein, and a pneumatic cuff connected to an automatic cuff inflator is placed around the leg below the transducer site. Reflux is provoked with rapid deflation of the cuff. Normal valves close rapidly after cuff deflation, and the reflux time rarely exceeds 0.5 seconds, except in the femoropopliteal veins, where the cut-off value of reflux should probably be 1.0 second (Labropoulos et al. 2003).

Reflex can also be elicited with release of manual calf compression (Coleridge-Smith et al. 2006). However, Yamaki et al. (2006) showed that although reflux times did not differ between the two methods, manual compression produced higher peak reflux velocities. In the groin and upper thigh, an adequate method to elicit retrograde flow is the Valsalva maneuver (Masuda et al. 1994a).

The most useful ways to express the duplex findings are diagrammatic representation and a textual report. The report should include the presence of incompetence at each saphenous junction, the extent of reflux in the saphenous trunks, and location of other diseased veins as well as their diameters. The diagram should also indicate the origin of recurrent varicose veins and the information regarding abnormal or removed veins as well as the patency and possible incompetence of previously thrombosed deep or superficial veins. The person who undertakes the investigation most often is a vascular technologist or a nurse, a vascular scientist, a radiologist, an angiologist, a phlebologist, or a surgeon. The UIP (the Union Internationale de Phlebologie) Consensus Document states that the informative process is facilitated, if the clinician responsible for the treatment performs the examination himself (Coleridge-Smith et al. 2006).

Duplex ultrasound has become the reference standard in evaluation of chronic venous disease (Coleridge-Smith et al. 2006). Several studies have shown that if the diagnosis of primary uncomplicated varicose veins is based on HDD examination alone, the proportion of patients who will receive inadequate or inappropriate operation ranges from 9 to 24% (Darke et al. 1997, Mercer et al. 1998, Rautio et al. 2002a). Duplex ultrasound best assesses the complex variations of venous anatomy and patterns of reflux in both primary and recurrent varicose veins as well as in chronic venous insufficiency (Jutley et al. 2001, Makris et al. 2006, Wong et al. 2003). Yet, duplex performance is dependent on the experience of the examiner. Whether routine use of preoperative duplex imaging improves the outcome of superficial venous surgery or reduces the recurrence rates remains controversial. Smith et al. (2002) showed in a randomized trial that preoperative marking of primary varicose veins with duplex ultrasound had no additional benefit over that of clinical and HDD marking at 12 months in terms of more accurate surgery, reduced recurrence rates, or improved quality of life. On the contrary, in another randomized
clinical trial with two years follow-up, routine preoperative duplex examination improved the outcome of surgery significantly (Blomgren et al. 2005a).

6.3 Phlebography

The role of contrast phlebography, historically considered as the gold standard method in the diagnosis of venous disease, has been drastically dropped with the widespread availability of the doppler techniques. Although ultrasound has largely replaced phlebography also for routine diagnosis of acute DVT, some indications still exist: indefinite duplex scan, iliofemoral venous thrombosis when thrombectomy is planned, and consideration of catheter-directed thrombolysis (Kamida et al. 2001). In diagnosis of chronic venous disease, ascending phlebography is still the most accurate method to differentiate primary venous disease from post-thrombotic disease, and descending phlebography is necessary for patients who are candidates for deep venous reconstructive surgery (Kamida et al. 2001). Videotaping (cine phlebography) enables real-time visualization of the flow dynamics. Phlebography is important in identifying the extent and nature of obstruction of the common femoral and iliac veins as well as in evaluation of the degree of reflux and the morphology of the valves. Compared to descending phlebography, in addition to being non-invasive and easily repeatable, duplex ultrasound is more sensitive in detecting both deep and superficial venous reflux below the knee (Baker et al. 1993).

6.4 Plethysmography and direct pressure measurements

Imaging modalities such as ultrasound and phlebography cannot assess the impact of reflux or obstruction on overall venous function. Plethysmography is the only practical non-invasive test for global physiologic evaluation of lower extremity veins (Meissner et al. 2007a); it is the best method to grade the severity of residual venous outflow obstruction and to non-invasively evaluate calf muscle pump function (Araki et al. 2001). Plethysmographic techniques provide information indirectly related to venous volume changes. Foot volumetry can provide the same information (Norgren 1974). Several plethysmographic techniques are in clinical use: air, photoelectric, strain-gauge, and impedance plethysmography as well as light reflection rheography (Araki et al. 2001). Ambulatory venous pressure is a product of venous obstruction, of reflux, and of calf muscle pump dysfunction, and represents the global measurement of venous insufficiency (Masuda et al. 2001). However, direct pressure measurements are invasive, and hence impractical. Non-invasive tests such as duplex ultrasound and plethysmography have largely replaced AVP testing. Venous pressures are measured by inserting a needle into a superficial dorsal foot or ankle vein, and having the patient perform toe lifts or other form of exercise in a standing position. Resting foot pressure represents the hydrostatic pressure. A normal pressure drop with exercise is greater than 50%, and normal refill time greater than 20 seconds (Masuda et al. 2001).
7 Treatment of chronic venous disease

7.1 Compression therapy

Despite the availability of numerous invasive treatment options, the primary mode of treatment of chronic venous disease remains compression therapy (Nicoloff et al. 2001). Limb compression has several beneficial effects, although the specific mechanisms remain unknown (Nicoloff et al. 2001). Compression reduces edema formation and increases edema resorption, reduces the caliber of the veins, reduces reflux, residual volume, and AVP, and improves the effectiveness of the calf muscle pump (Felty et al. 2005).

The various compression modalities include elastic compression stockings, paste gauze boots (Unna boot), simple elastic wraps, multilayered wrapped dressings, and inelastic legging orthosis (the CircAid device), as well as external pneumatic compression devices (Nicoloff et al. 2001). The most widely used form of compression has been elastic compression stockings, which provide distally increasing compression of 20 to 60 mmHg. Even lightweight gradient compression stockings (8-20 mmHg) are effective in improving venous-related symptoms such as discomfort, swelling, fatigue, aching, and leg tightness (Weiss et al. 1999). Hirai et al. (2002) demonstrated edema prevention in patients with varicose veins with low-compression stockings, although the effect was better with higher compression (22-40 mmHg). Patients with venous ulceration should use the highest level of compression that is comfortable. Nelson et al. (2006) compared in a randomized trial class 2 (18-24 mmHg) and class 3 (25-35 mmHg) elastic compression in prevention of recurrence of venous ulceration. They found no significant difference in recurrence rates, but estimated that the lower compliance rate among patients using higher compression diluted the effectiveness of class 3 hosiery.

The ESCHAR trial demonstrated that compression therapy is as effective as surgery in healing venous ulcers (Gohel et al. 2007). In this trial, open ulcers were treated with multilayered compression bandages aiming at 40 mmHg of pressure, and healed ulcers with class 2 elastic stockings. Yet, compression therapy was inferior to superficial venous surgery in reducing ulcer recurrences (Gohel et al. 2007).

7.2 Superficial venous surgery

7.2.1 Indications and planning

The usual indications for venous surgery include general appearance, aching pain, leg heaviness, easy leg fatigue, superficial thrombophlebitis, external bleeding, and skin changes related to venous insufficiency (Bergan 2001). Prerequisites for surgery are always evaluated individually, with assessment of potential risks related to operative treatment as well as to the attainable benefits. Although superficial venous surgery can be, and in many places still is, performed without any objective evaluation of the extent and sites of venous incompetence, the complex nature of venous disease warrants careful
preoperative examination in order for the surgery to be adequate. As stated earlier, duplex ultrasound scanning is currently recommended before all operations for varicose veins (Mercer et al. 1998). In addition, accurate marking of the insufficient veins, of the termination of the small saphenous veins, if incompetent, as well as marking the varicosities on the patient’s skin immediately before the operation assures the removal of the right veins and location of the sapheno-popliteal junction (Bergan 2001).

7.2.2 Surgical procedures

The main purpose of superficial venous surgery is to eliminate venous reflux and to correct the pathological venous hemodynamics. The preoperative evaluation determines the proper surgical procedure for each patient. If the SFJ and the GSV are incompetent, adequate surgery includes flush ligation of the SFJ (Homan 1916) and groin-to-knee stripping of the GSV (Cheatle 2005, Meissner et al. 2007b). If the GSV system is competent, it should be left intact (Bergan 2001). Almost all superficial venous operations are supplemented by stab avulsions of distal varicosities. Performing the operations in a bloodless field using a proximal (e.g. Boazul) cuff reduces subcutaneous extravasation of blood, which is a major cause of discomfort, and occasional permanent skin pigmentation (Robinson et al. 2000). Use of high-volume, dilute tumescent anesthesia also minimizes extravasation (Meissner et al. 2007b).

Several authors have demonstrated that ligation of the SFJ without GSV stripping is ineffective in controlling reflux, and recurrence after such an operation is more common than after ligation and stripping (Dwerryhouse et al. 1999, Jones et al. 1996, McMullin et al. 1991, Sarin et al. 1994b). Compared to traditionally performed ankle-to-groin stripping, retrograde perforate-invaginate stripping (PIN-stripping) (Oesch 1993) seems to cause less postoperative morbidity (Goren et al. 1994). This technique is a modification of other techniques of inverted stripping (Staelens et al. 1992, van der Stricht 1963) and involves invagination of the vein without the need for the relatively traumatic passage of an olive at the end of a conventional stripper. In addition, Holme et al. (1990) have shown that stripping the GSV only to the knee level reduces the risk for saphenous nerve damage.

In most cases, reflux in the distal part of the GSV is not clinically important (Dwerryhouse et al. 1999, van Neer et al. 2006), and after groin-to-knee stripping of GSV may even cease (Blomgren et al. 2005b). However, a recent study by Kostas et al. (2007) found no significant difference in rate of saphenous nerve injury between total and groin-to-knee stripping of GSV. The authors concluded that “the appropriate length of great saphenous vein stripping should be based on the extent of reflux and not on the intent to avoid saphenous nerve injury”.

SSV surgery is technically more challenging due to the variability of the anatomy of the termination, and proximity of the suralis nerve to the vein in the ankle (Bergan 2001). Because SSV reflux is often segmental and the distal part competent, PIN-stripping to a point just below halfway down the calf is usually sufficient (Oesch 1993).

Controversy exists over the treatment of incompetent perforating veins. Some surgeons claim that in patients with CVI interruption of IPVs is necessary (Gloviczki et al. 1999, Iafrati et al. 2002), whereas others suggest that superficial vein ablation alone is often
sufficient to improve the hemodynamics, and may also abolish incompetence in perforating veins (Blomgren et al. 2005b, Gohel et al. 2005a, Mendes et al. 2003). Stuart et al. (1998) showed, however, that in the presence of deep venous incompetence, saphenous surgery fails to correct perforator incompetence.

Back in 1938 Linton described the operation of subfascial ligation of the medial lower leg communicating veins. This classic approach used ligation of all perforating veins between the posterior tibial border and the midline posteriorly via a long vertical incision into the fascia (Linton procedure). This operation has many disadvantages, including poor healing of the longitudinal incision (DePalma 2001). It is easy to demonstrate with duplex ultrasound that all perforators are not alike. While some can be insufficient and refluxing, others may function adequately. Ligation of these normal perforators may be harmful. In 1953, Cockett described the “ankle blow-out syndrome” and its treatment by the extrafascial ligation of incompetent communicating veins. Although several surgeons modified the original techniques, a major change in clinical practice occurred only after the introduction of subfascial endoscopic perforator surgery (SEPS). Hauer reported this technique of perforating vein division using an endoscope in 1985. Although several reports have demonstrated clear benefits of SEPS in terms of ulcer healing and low complication rates (Nelzén et al. 2007, Tenbrook et al. 2004), the meaning and efficacy of perforating vein interruption, regardless of the technique, remains controversial.

### 7.2.3 Complications

Although superficial venous surgery is one of the most common surgical operations, the true risks associated with this operation remain poorly documented. Critchley et al. (1997) reported complications related to varicose vein operations in a series of about 600 patients. In this retrospective review, the rate of major complications was extremely low: 0.8%, with minor complications occurring in 17%. Complications associated with superficial venous surgery include ecchymosis, lymphocele, wound infections, injuries to cutaneous nerves, and injuries to arteries, as well as deep venous thrombosis and pulmonary embolism (Critchley et al. 1997).

The most frequent complication after GSV stripping is saphenous neuralgia (Puggioni et al. 2005). The symptoms include sensory loss on the medial aspect of the calf above the medial malleolus, numbness, tingling, and pain. In most patients, the area of paraesthesia improves over time, but some will develop chronic pain syndrome. The incidence, etiology, natural history, prevention, and management of this condition are unknown (Sam et al. 2004a). When the standard practice was to strip the GSV from ankle to groin, the rate of nerve injury reached 50% (Cox et al. 1974, Munn et al. 1981). According to a review article by Sam et al. (2004a), stripping in a retrograde fashion reduces the rate to 4 to 23%. Restricting the stripping to just below the knee results in a short-term nerve injury rate of 7 to 9% (Durkin et al. 1999, Holme et al. 1990). With inversion stripping, the rate of neuralgia has been 0 to 13% (Butler et al. 2002, Lacroix et al. 1999). Numerous factors limit the interpretation of these data, such as small sample size, and short follow-up, as well as lack of detailed information about the postoperative assessment (Sam et al. 2004a). Even less is known about the incidence of sural nerve injury associated with SSV
stripping. Number of case reports have described this complication, but the true risk remains unclear (Mondelli et al. 1997, Simonetti et al. 1999). The symptoms are the same as in saphenous neuralgia, but the location is on the lateral aspect of the calf above the lateral malleolus.

Saphenous and suralis nerve injury may also occur after SEPS, but the risk associated with this operation is difficult to assess, because SEPS is often performed in conjunction with GSV or SSV surgery or both (Sam et al. 2004a).

The most serious complication after superficial venous surgery is DVT and fatal pulmonary embolism. The true incidence is unknown. The incidence of clinically diagnosed DVT after varicose vein surgery in two studies was 0.15 to 0.5% (Critchley et al. 1997, Hagmuller 1992). The incidence of DVT was higher in a recent prospective study with routine postoperative duplex scanning: 5.3% (van Rij et al. 2004a). Short and long-term clinical significance was minimal, and none of the patients with DVT developed PE. Bhogal and Nyamekye (2008) evaluated whether the occurrence of leg swelling within 6 weeks of surgery could determine the need for duplex imaging. The incidence of swelling was 8.9%, and of duplex-confirmed DVT 1.3%. All patients with leg swelling underwent duplex examination. None without swelling developed any leg problems. The authors concluded that this policy detected all clinically significant DVTs and generated only manageable workloads (Bhogal et al. 2008).

7.2.4 Outcome of surgery

In general, superficial venous surgery is advantageous in terms of symptomatic relief, and reduction of ulcer recurrences, as well as in improvement of both generic and disease-specific health-related quality of life (Gohel et al. 2007, Michaels et al. 2006, Sam et al. 2004b, Smith et al. 1999). Surgery results in a hemodynamic benefit for legs with venous ulceration as well as for those with uncomplicated CVD (Bergan 2001, Gohel et al. 2005b). A recent randomized trial has also demonstrated that surgery for uncomplicated varicose veins is cost effective, and compared to conservative treatment, offers a modest health benefit for relatively little additional cost (Ratcliffe et al. 2006).

Recurrence of varicose veins

A common and complex problem associated with varicose vein operations is recurrence (Perrin et al. 2000). An international consensus group has defined recurrent varices after surgery (REVAS) as “presence of varicose veins in a lower limb previously operated on for varices” (Perrin et al. 2000). Thus, these strict criteria for REVAS include true recurrences, residual refluxing veins, and varicose veins caused by disease progression. The estimated rate of clinical recurrence is between 20 and 80%, and depends on the definition and the duration of follow-up (Perrin et al. 2000). Van Rij et al. (2003) have shown that the rate of recurrence increases with time. In their small prospective trial of 92 consecutive patients, the recurrence rate increased from 14% at 3 months to 52% at 3 years. As a consequence of high recurrence rates, approximately 20% of all varicose vein
operations are for recurrent disease, although the average time until redo surgery is usually long, ranging from 6 to 20 years (Perrin et al. 2000).

Although recurrence after varicose vein surgery is common, most patients remain satisfied (Winterborn et al. 2004). However, the majority of patients with REVAS are symptomatic despite improved clinical scores (Allegra et al. 2007, Kostas et al. 2004, Perrin et al. 2006). In patients who have undergone superficial venous surgery for venous ulceration, residual venous reflux does not necessarily predict ulcer recurrence (Kulkarni et al. 2007), although total elimination of incompetent superficial and perforating veins lowers this risk (Magnusson et al. 2006).

Factors predisposing to recurrence


Although duplex ultrasound currently allows accurate preoperative diagnostics, recurrence continues to be a problem (Allegra et al. 2007, Kostas et al. 2004, Smith et al. 2002, van Rij et al. 2003). Allegra et al. (2007) demonstrated this in a prospective study of 1326 patients: Despite preoperative duplex scanning, the recurrence rate at 5 years was 25%. No residual reflux occurred at the 3-week duplex scan, which ascertained technically correct surgery.

In general, surgery may be inadequate due to either technical or tactical failure (Perrin et al. 2006). An incorrect procedure, e.g., inadequate ligation of the SFJ or incomplete stripping of the GSV, is usually classified as a technical failure, and inappropriate surgery, e.g., SFJ ligation without stripping the incompetent GSV, as a tactical failure (Kostas et al. 2004, Perrin et al. 2006). Disease progression refers to development of new sites of venous reflux in previously normal veins and accounts for about 25 to 30% of recurrences (Kostas et al. 2004, Perrin et al. 2006).

Neovascularization refers to the presence of thin, serpentine veins at a previously ligated SFJ or SPJ (Kostas et al. 2004, Perrin et al. 2006). Neovascularization as a cause of recurrence has been under intensive debate. Many reports have provided clinical, ultrasound, and histological evidence that formation of these serpentine tributaries at the SFJ is the principal cause of REVAS (Jones et al. 1996, Nyamekye et al. 1998, van Rij et al. 2004b), whereas others consider this phenomenon rarely to be the single cause of recurrence (Egan et al. 2006, Turton et al. 1999). El Wajeh et al. (2004) analyzed previously ligated SFJs histologically, found little evidence of neovascularization, and concluded that venous channels that develop to ligated SFJ may represent adaptive dilatation of pre-existing venous channels rather than neovascularogenesis.

Attempts to prevent neovascularization after groin dissection by constructing an anatomic or prosthetic barrier, using a patch to cover the ligated SFJ, have been somewhat promising (De Maeseneer et al. 2002, De Maeseneer et al. 2004, Earnshaw et al. 1998).
a recent randomized controlled trial evaluating mechanical suppression of neovascularization at the SFJ, a PTFE patch halved the recurrence rate to 3 years postoperatively in all clinical subgroups (van Rij et al. 2008). Another attempt, with complete resection of the GSV stump combined with endothelial inversion, failed to reduce neither neovascularization nor thigh varicosity recurrence (Heim et al. 2008).

Stücker et al. demonstrated in two separate studies that the most common mechanism of recurrent saphenofemoral junction reflux after SFJ ligation and GSV stripping is original misidentification of the SFJ, as evidenced by an identifiable GSV stump in two-thirds of the symptomatic groins (Geier et al. 2008, Stücker et al. 2004). The authors conclude that a residual stump left in place at the initial operation seems to be associated with symptomatic REVAS, and better supervision and training may prove more effective in reducing the incidence of recurrent SFJ reflux than are surgical maneuvers directed at reducing neovascularization.

Anatomic patterns of reflux in REVAS

Studies that evaluate anatomic patterns of reflux in REVAS are difficult to compare because of differences in the definition of recurrence, and in the initial treatment and preoperative evaluation, as well as in the method and duration of follow-up. Although the international consensus group has developed a classification for patients with REVAS to be used as a complement to the CEAP (Perrin et al. 2000), only a few studies so far have used this classification for reporting the outcomes (Kostas et al. 2004, Perrin et al. 2006). Stonebridge et al. evaluated varicograms of recurrent legs and based on these, described a classification for groin recurrences in Edinburgh in 1995. Other reports have used this earlier classification as well, but some authors have found it difficult to classify the anatomy of recurrence in the groin according to this Edinburgh system (Blomgren et al. 2004).

A uniform finding in studies evaluating the sites of incompetence in REVAS is the presence of multiple patterns of reflux. The most common source of incompetence is the SFJ. The rates of incompetent perforating veins as well as the frequency of deep venous incompetence in patients with REVAS vary greatly between studies (Table 7).

7.3 Ambulatory conservative hemodynamic management of varicose veins (CHIVA)

In 1988, Franceschi described conservative hemodynamic management of CVD, known as CHIVA (Cure Conservatrice et Hémodynamique de l’Insuffisance Veineuse en Ambulatoire). This consists of minimally invasive surgical procedures using duplex imaging, based on hemodynamic analysis of the venous network. The aim of CHIVA is to relieve the hydrostatic pressure column by interruption of the venovenous shunts of the GSV or other superficial veins that create recirculation of venous blood between the deep and the superficial system. The GSV itself and re-entry perforating veins are left intact to
**Table 7.** Ranges of reflux rates for the most common sources of incompetence in recurrent varices after surgery

<table>
<thead>
<tr>
<th>Source of venous incompetence</th>
<th>Follow-up (years)</th>
<th>Reflux rate (%)</th>
<th>References</th>
</tr>
</thead>
</table>

*No preoperative duplex, ** preoperative duplex

SFJ, sapheno-femoral junction; SPJ/SSV, sapheno-popliteal junction / small saphenous vein

Act as a route of venous drainage (Juan et al. 2005). Treatment strategy depends on the type of venovenous shunting (Zamboni et al. 2003).

Results vary between studies: A 3-year prospective study by Escribano et al. (2003) showed that elimination of reflux in the GSV after interruption of insufficient collaterals was only temporary, with reflux in 92% of the GSVs. A recent randomized trial comparing the outcome of saphenous stripping and CHIVA after a mean follow-up of 10 years demonstrated that recurrent varices occurred more frequently following stripping than after CHIVA (Carandina et al. 2008). Another randomized trial by Zamboni et al. (2003) showed a significant advantage for CHIVA over compression alone in patients with venous ulceration. Thus, this minimally invasive technique appears to be an alternative treatment for patients unfit for traditional surgery and with complicated venous disease.
7.4 Endovenous techniques

Postoperative morbidity and high recurrence rates related to superficial venous surgery, as well as the problems associated with reoperations, have led to development of new endovascular treatments. These are increasingly replacing traditional surgery as the treatment of choice. Currently, widely used techniques include ultrasound-guided foam sclerotherapy (UGFS) and endovenous laser therapy (EVLT), as well as radiofrequency ablation (RFA).

7.4.1 Ultrasound-guided foam sclerotherapy

Sclerosing foam is a mixture of gas and liquid sclerosing solution with tensio-active properties (Frullini et al. 2002). Orbach introduced the concept of foam sclerotherapy in 1944: the air block technique. He added sclerosing solution to air by shaking the syringe with production of large bubbles. This method was suitable only for small veins. Several authors described different techniques over the years (Wollmann 2004), but it was not until 1997, when Cabrera published an article on the production of microfoam, that foam sclerotherapy became a method of increasing interest. In the same year, Montfreux described a method that generated simple foam with air by means of a glass syringe.

In 2000, Tessari published an original method of foam production using two disposable syringes and a three-way tap. He demonstrated in a pilot study that the technique is promising, especially for larger veins (Tessari et al. 2001). In 2000, Frullini published a new technique to produce foam in a disposable vial of sclerosant with the air contained in the vial, or with prior withdrawal of 2 ml of sclerosing solution. The author claims that this method minimizes the possibility of contamination. Currently, the Tessari method or the modified Tessari/DSS (Double Syringe System) are the techniques most commonly used (Breu et al. 2008).

In liquid sclerotherapy, blood dilutes the sclerosant before contact with the endothelium. Foam sclerosants, in contrast, displace blood in the vein lumen, allowing direct contact with the vein wall. This causes disruption of the endothelial cells, which induces an intense spasm in the vein (Raju et al. 2004). Subsequent fibrosis leads to destruction of the vessel. Several studies have shown that in the treatment of superficial venous incompetence, sclerotherapy with foam is more effective than with liquid (Alos et al. 2006, Hamel-Desnos et al. 2003, Yamaki et al. 2004). The most common sclerosing agents are sodium tetradecyl sulfate (STS) and polidocanol (POL), which are mixed with air, oxygen, or carbon dioxide (CO₂) (Breu et al. 2008). In a recent study by Morrison et al. (2008), using CO₂ rather than air to make the sclerosing foam reduced immediate adverse events significantly. The most often used concentrations of POL and STS are between 1 and 3%. In principal, the larger the diameter of the vein, the more viscous the foam should be (Breu et al. 2008).
**Indications and contraindications**

The indications for UGFS are essentially the same as those for surgery. Both primary and recurrent varicose veins, GSVs, SSVs, tributaries, and perforating veins principally in all calibers are suitable for this treatment. Other indications for UGFS include reticular veins, teleangiectasies, venous malformations, vulvar varices, hemorrhoids, and Baker’s cysts (Breu et al. 2008).

Absolute contraindications include allergy to the sclerosant or acute deep or superficial venous thrombosis. Most experts think that a known symptomatic patent foramen ovale (PFO) is an absolute contraindication. The average prevalence of PFO in the general population is 26% (Meier et al. 2003). Patients with known asymptomatic PFO should be treated with special care because of the possibility of pulmonary toxicity and central nervous system complications. Relative contraindications include a history of thromboembolism, high risk of thromboembolism, and known thrombophilia (Breu et al. 2008).

**Technique**

The second European consensus statement has made the following recommendations regarding UGFS (Breu et al. 2008): Guidance by ultrasound imaging is mandatory for direct puncture and injection of non-obvious GSV, SSV, perforating veins and other non-obvious varicose veins in the groin or popliteal fossa. The insufficient vein is visualized and punctured with a needle. Although the majority of experts think that during UGFS leg elevation is not mandatory, elevation is useful to reduce vein diameter. According to a recent study, elevation with no pressure at the SFJ also reduces the risk of gas embolization (Hill et al. 2008).

The foam is prepared immediately before the injection by mixing sclerosant and a well-tolerated gas in the desired ratio, which is usually 1:3 or 1:4 depending on the agent and on personal preferences. The amount of foam needed to fill the vein depends on the vein size. Usually the maximum amount of foam injected per session is limited to 10 ml. In the treatment of trunk veins, the foam may be directly injected or delivered by means of a catheter with or without an occlusive balloon just below the SFJ. The foam is echogenic, which allows visualization of the spreading of the foam and of the replacement of blood in real time (Breu et al. 2008).

The need and duration of post-treatment compression remain controversial, and no consensus exists. The majority of the experts use whole-leg compression after the treatment of GSV, SSV, and recurrent varicose veins (Breu et al. 2008).
### Table 8. Rates of adverse events of ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial events (stroke, thromboembolic events)</td>
<td>0-2.8</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0-5.7</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0-0.3</td>
</tr>
<tr>
<td>Cutaneous necrosis</td>
<td>0-2.6</td>
</tr>
</tbody>
</table>

**Adverse events**

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual disturbance</td>
<td>0-6</td>
</tr>
<tr>
<td>Transient confusion</td>
<td>0-1.2</td>
</tr>
<tr>
<td>Headache</td>
<td>0-23</td>
</tr>
<tr>
<td>Other systemic symptoms (coughing, chest tightness / heaviness, panic attack, malaise, vasovagal)</td>
<td>0-2.8</td>
</tr>
<tr>
<td>Minor vein thrombosis</td>
<td>0-18</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0-46</td>
</tr>
<tr>
<td>Matting / skin staining / pigmentation</td>
<td>0-66.7</td>
</tr>
<tr>
<td>Local neurological injury</td>
<td>0-0.7</td>
</tr>
<tr>
<td>Pain at the site of injection</td>
<td>0.6-41</td>
</tr>
<tr>
<td>Others (local allergic reaction, hematoma, extravasation, lower back pain)</td>
<td>0-11.2</td>
</tr>
</tbody>
</table>

### Complications

A recent systematic review (including RCTs, case series, and registries, as well as conference abstracts) assessed the safety and efficacy of foam sclerotherapy in the treatment of teleangiectatic, reticular, and varicose veins (Jia et al. 2007) (Table 8). Serious adverse events occurred in 0 to 5.7% of treatments. A case report described a stroke that a 61-year-old man developed shortly after UGFS (Forlee et al. 2006). A transoesophageal echocardiogram revealed a PFO and a right-to-left shunt. Overall, serious neurological complications after UGFS are rare, occurring in 2% or less of patients (Forlee et al. 2006, Guex et al. 2005).

### Outcome

In studies evaluating the results of UGFS, efficacy outcomes include occlusion of the treated vein, elimination of venous reflux, healing of venous ulcers, recurrence of venous disease and development of new veins, QoL, disappearance of varicosities, and changes in disease severity, as well as procedure time (Jia et al. 2007). This variability in efficacy outcomes makes it difficult to compare studies. To standardize the reporting in future studies, the second consensus committee meeting on foam sclerotherapy set efficacy criteria for UGFS (Breu et al. 2008) (Table 9).
Table 9. Definition / grading of therapeutic effects of Foam Sclerotherapy (Breu et al. 2008) (© 2008 by Verlag Hans Huber, reprinted with permission from the publisher)

<table>
<thead>
<tr>
<th>Grading / Name</th>
<th>Duplex findings</th>
<th>Clinical</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 FULL SUCCESS</td>
<td>NO REFLUX</td>
<td>a) complete disappearance of the treated vein or “fibrous cord” (incompressible echogenic cord in the position of the treated vein) b) complete occlusion (incompressibility) of the treated vein segment c) patency of the treated vein segment with reduced diameter and antegrade flow</td>
<td>normalised (i.e. no visible varices)</td>
</tr>
<tr>
<td>1 PARTIAL SUCCESS</td>
<td>REFLUX &lt; 1 sec.</td>
<td>partial incompressibility and partial occlusion of the treated vein segment and diameter reduction</td>
<td>normalised or improved (i.e. smaller visible varices)</td>
</tr>
<tr>
<td>0 NO SUCCESS</td>
<td>REFLUX &gt; 1 sec. or unchanged</td>
<td>complete (or incomplete) patency and/or no change in diameter</td>
<td>unchanged or worsened (i.e. larger varices and/or clinical CEAP deterioration)</td>
</tr>
</tbody>
</table>

Additional information
- Duplex evaluation is performed in an upright position
- The length of the occluded vein must be compared with the length of the insufficient part of the vein which was injected with the aim of occlusion (before injection it should be decided which part of the vein is intended to be treated). This is important for the question whether the “whole vein” is occluded after treatment
- Reflux is measured with the Valsalva manoeuvre or distal compression / decompression
- With reference to symptoms – if applicable – more differentiated and standardised symptom scores like the VSS can be used, otherwise the VAS (visual analogue scale 1–10) can be very useful and simple
- With reference to clinical findings – if applicable – more differentiated and standardised classifications such as CEAP can be used
- The definitions and gradings are applicable for all endovenous procedures (endovenous laser, radiofrequency ablation and sclerotherapy) and should allow comparison
- In the case of simultaneous treatment for medical and for aesthetic reasons, two separate questionnaires should be used
- The number of treatments (injections, sessions) and the kind of treatment used should be recorded
### Table 10. Outcome of ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Rate (range) (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion of the treated vein (follow-up ≥ 6 months)</td>
<td>Weighted mean 80.6 (68-86)</td>
<td>(Barrett et al. 2004a, Barrett et al. 2004b, Cabrera et al. 2000, Coleridge-Smith 2006, O'Hare et al. 2008, Wright et al. 2006, Yamaki et al. 2004)</td>
</tr>
<tr>
<td>Ulcer healing</td>
<td>Median rate 80.5 (75-100)</td>
<td>(Jia et al. 2007)</td>
</tr>
<tr>
<td>Recurrence / development of new veins</td>
<td>Median rate 8 (0.5-51.2)</td>
<td>(Jia et al. 2007)</td>
</tr>
</tbody>
</table>

Weighted mean = number of patients/limbs with occlusion/reflux in each study divided by total number of patients/limbs

The immediate occlusion rate after a single session of UGFS is nearly 90%, and the proportion of patients requiring more than one session is 8 to 15% (Cabrera et al. 2000, Darke et al. 2006, O'Hare et al. 2008, Wright et al. 2006). The occlusion rate slightly deteriorates during follow-up (Table 10).

Barrett et al., whose recanalization rates have been the lowest, has reported high patient satisfaction and improved QoL (Barrett et al. 2004a, 2004b). All patients in these studies believed that UGFS had been successful in treating their varicose veins and related symptoms, and over 90% reported improved QoL.

Some authors have combined UGFS with surgery (Bountouroglou et al. 2006, Creton et al. 2007). The former reported total or partial occlusion of the GSV at 3 months after UGFS with 3% STS and SFJ ligation in 87%; the latter combined peroperative UGFS with 1% POL and surgery for recurrent varicose veins, and concluded that UGFS facilitates surgical treatment. At 40 days, the rate of complete obliteration of saphenous trunks was 93%.

Myers et al. (2007) have analyzed factors that affect the outcome of ultrasound-guided sclerotherapy. In that study, liquid sclerosant (STS or POL) was used in approximately 8% of the sessions. Primary success for all veins was worse for saphenous veins than for tributaries. Cox regression for all saphenous veins showed worse results for patients younger than 40, small compared to great saphenous veins, veins greater than 6 mm in diameter, liquid compared to foam sclerotherapy, lower volumes of sclerosant compared to volumes greater than 12 ml, and highly diluted or undiluted 3% sclerosant compared to a 1.5% concentration. A previous operation for varicose veins or a commercial type of sclerosant did not affect outcome (Myers et al. 2007).
In a 2006 study by Coleridge-Smith, the outcome was similar after great and small saphenous vein treatment as well as in patients with recurrent varices. In addition, Barrett et al. (2004a) compared the results in a subgroup with diameters at the SFJ or SPJ of 10 mm or greater to a subgroup with diameters less than 10 mm, and concluded that UGFS is effective in treating all sizes of varicose veins. Although the incidence of failure to close the junction was higher in the ≥10 mm group, this difference did not translate to clinical recurrence. Hamel-Desnos et al. (2007) compared the efficacy of 1% and 3% POL foam in a single session of UGFS of the GSV using elimination of venous reflux as the main criterion of success. At 2 years, no difference occurred between the groups: The success rate for 1% POL was 68%, and for 3% POL 69%.

### 7.4.2 Endovenous laser therapy

In 2001, Navarro et al. and Min et al. published the first cohort studies that demonstrated EVLT to be an effective treatment for great saphenous vein incompetence. Later, EVLT has proven effective in eliminating small saphenous vein reflux as well as incompetent perforating veins (Proebstle et al. 2003, 2007, Theivacumar et al. 2007). The mechanism of EVLT is not entirely clear, but laser-induced direct and indirect thermal reactions seem to be essential (van den Bos et al. 2008). They cause scar formation and occlusion of the vein.

A systematic review has assessed the safety and effectiveness of endovenous laser treatment (Mundy et al. 2005), with the adverse events of EVLT including incorrect positioning of the laser, superficial skin burns, DVT, ecchymosis, hyperpigmentation, saphenous paraesthesia, induration, phlebitis, pain, hematoma, and bruising.

The main measure of the effectiveness of EVLT is abolition of reflux demonstrated by complete occlusion or obliteration of the treated vein (Mundy et al. 2005). Occlusion rates vary among studies, with a follow-up of a mean 28 days to 19 months from 87.9 to 100%, and the rate of recanalization from 0 to 4.8% (Mundy et al. 2005). The immediate success rate in most studies is 100%, and although the success rate decreases with time, it remains at least 90% (van den Bos et al. 2008). Similarly, a large study with 1000 patients and 3 years’ follow-up reported a success rate of 97% (Agus et al. 2006).

Theivacumar et al. (2008a) assessed changes in GSV diameter and the significance of recanalization, and concluded that a recanalized GSV usually remains small with no or minimal reflux and persisting clinical benefit. Kim et al. (2006) have demonstrated that larger GSV diameter is associated with early treatment failures. Labropoulos et al. (2006) reported small arterio-venous fistulae formation within the obliterated vein after EVLT, and suggested that this process may be responsible for recanalization or recurrence.

Some authors have combined EVLT with high ligation of the SFJ, and conclude that this method is safe and effective, achieves cosmetic goals, and reduces symptoms associated with varicose veins (Kalteis et al. 2008, Lu et al. 2008). Huang et al. (2005) successfully combined EVLT with various surgical strategies in patients with primary superficial or deep venous incompetence.

Because the EVLT procedure does not treat tributary varicosities, many patients need further foam sclerotherapy or phlebectomy (Gough et al. 2007). Theivacumar et al.
(2008b) demonstrated recently that residual varicose veins are more common in patients who have undergone standard above-knee GSV EVLT compared to those who have had EVLT from mid-calf to groin. The percentages of limbs with refluxing below-knee GSV at 6 weeks in standard and extended EVLT groups were 52% and 0%. The complication rates between the groups did not differ, and no patients in either group developed saphenous nerve injury. The authors thus concluded that “extended EVLA [endovenous laser ablation] is safe, increases spontaneous resolution of varicosities, and has a greater impact on symptom reduction”.

7.4.3 Radiofrequency ablation

In 2000, Goldman described endovenous radiofrequency ablation (Closure system: VNUS Medical Technologies Inc. Sunnyvale, CA, USA) of the GSV. Radiofrequency produces direct heating of the vein wall, which leads to collagen denaturation, and acute vein constriction (Beale et al. 2005, Goldman 2000). Previous attempts to eliminate reflux endovenously had relied on electrocoagulation of blood, which led to thrombus formation and occlusion of the vein with potentially high rate of recanalization (Goldman 2000). A single manufacturer has made the RFA catheter (the Closure® catheter) and has a standardized application protocol (Stirling et al. 2006).

The procedure may be combined with phlebectomy and sometimes with SFJ ligation. Chandler et al. (2000) showed in a prospective comparative study that “extended SFJ ligation may add little to effective GSV obliteration”. In the study by Monahan et al. (2005), GSV ablation with RFA resulted in resolution or regression of approximately 90% of varicose veins. Welch showed in 2006 that “an algorithm of reassessment of the limb and branch varicosities several months post-RFA allows most patients to defer stab phlebectomy”.

Complications of RFA include paresthesia, skin burns, hematoma, infection, thrombophlebitis, DVT and PE (Beale et al. 2005, Stirling et al. 2006).

Five-year results from a prospective multicenter study are available (Merchant et al. 2005). This study included 1006 patients with 1222 limbs from 34 centers. Of these, only 117 limbs were available for the last follow-up. Most treated veins were above-knee GSVs (89.1%). At each annual follow-up, the occlusion rates of all treated veins were 87.1%, 88.2%, 83.5%, 84.9%, and 87.7%. The rate of absence of reflux decreased from 88.2% at one year to 83.8% at 5 years. Symptom improvement was common also in limbs with anatomical failures: 70% to 80% of the limbs with failure improved clinically compared to 85% to 94% of the limbs with anatomical success. The rate of varicose vein recurrence increased from 13.1% at one year to 27.4% at 5 years (Merchant et al. 2005). Nicolini presented in 2005 limited 3-year results from the same multicenter registry. He demonstrated that no difference in clinical outcomes existed between limbs with total or partial occlusion. The risk for recurrence increased, if the length of the open segment exceeded 5 cm. Other groups have reported similar success rates; the rates of vein occlusion at one or 2 years have been 88 to 90% (Pichot et al. 2004, Sybrandy et al. 2002, Weiss et al. 2002).
The mode of action of RFA causes a significantly prolonged treatment time if compared with EVLT. The VNUS ClosureFast® segmental ablation catheter overcomes this disadvantage (Proebstle et al. 2008); In that prospective case series, the occlusion rate following segmental RFA of the GSV at 2 years was 99.6%.

7.4.4 Comparative studies

Prospective randomized controlled trials comparing the outcome of superficial venous surgery to the outcomes of the new endovenous techniques are still scarce, as are studies comparing the new treatments to each other. Few RCTs have compared foam sclerotherapy to surgery, to sclerotherapy, or to combined treatment (Belcaro et al. 2003, Bountouroglou et al. 2006, Wright et al. 2006).

The VEDICO trial compared six treatment options in patients with uncomplicated primary varicose veins (Belcaro et al. 2003) (Table 11). In all treatment groups, the decrease in AVP and increase in refilling time as well as the number of points of major incompetence were comparable. The authors concluded that “when correctly performed, all treatments may be similarly effective. "Standard," low-dose sclerotherapy appears to be less effective than high-dose sclero and foam-sclerotherapy which may obtain, in selected subjects, results comparable to surgery” (Belcaro et al. 2003).

A European randomized controlled trial compared ultrasound-guided foam sclerotherapy with Varisolve® polidocanol microfoam with surgery or sclerotherapy in patients with primary or recurrent C2-C4 venous disease (Wright et al. 2006) (Table 11). Varisolve® microfoam is a uniform foam of oxygen and carbon dioxide combined with 1% polidocanol. Surgical treatment included high ligation in 91.5% of the patients, stripping in 88.3%, and avulsion phlebectomy in 53.2%. In the sclerotherapy group, polidocanol or STS was in the form of foam in 92% of the cases, and the concentrations varied from 0.5% to 3%. Patients underwent central randomization to either the Varisolve® technique or alternative treatment (Varisolve® cohort vs. surgery and Varisolve® cohort vs. sclerotherapy). In the original publication, Varisolve® cohorts were analyzed separately, but presented here as one group (Table 11). In the Varisolve® vs. surgery cohort, the median time to resumption of normal activities after treatment was significantly shorter in the Varisolve® group than in the surgery group (2 vs 13 days) (Wright et al. 2006).

Bountouroglou et al. (2006) compared UGFS combined with SFJ ligation to surgical treatment (stripping and multiple avulsions) of primary varicose veins (Table 11). Elimination of reflux was not included as an endpoint. Patients in the UGFS + ligation group returned to normal activities significantly sooner, and had comparable QoL improvement and complication rates. The cost of this procedure was almost half for patients in the UGFS + ligation group (Bountouroglou et al. 2006).
### Table 11. RCTs comparing foam sclerotherapy and surgery: characteristics, endpoints and results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment groups</th>
<th>Patients (limbs)</th>
<th>Treated vein</th>
<th>FU</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEDICO (Belcaro et al. 2003)</td>
<td>A. sclerotherapy</td>
<td>123 (221)</td>
<td>SFJ (GSV)</td>
<td>10 y</td>
<td>- incompetent veins (recurrent or new veins) at 5 and 10 years</td>
<td>Incompetent veins at 5 years: A. 48% B. 41% C. 34% D. 40% E. 44% F. 34%</td>
</tr>
<tr>
<td></td>
<td>B. high-dose sclerotherapy</td>
<td>112 (222)</td>
<td></td>
<td></td>
<td>- variations in AVP and refilling time</td>
<td>at 10 years: A. 56% B. 49% C. 38% D. 41% E. 51% F. 37%</td>
</tr>
<tr>
<td></td>
<td>C. multiple ligations</td>
<td>132 (239)</td>
<td></td>
<td></td>
<td>- presence of duplex-reflux</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. stab avulsions</td>
<td>122 (244)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>E. foam sclerotherapy</td>
<td>129 (211)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. surgery (ligation) and sclerotherapy</td>
<td>131 (234)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European RCT (Wright et al. 2006)</td>
<td>1. Varisolve®</td>
<td>435</td>
<td>GSV or SSV</td>
<td>1 y</td>
<td>- response to treatment at 3 months (occlusion/absence of the treated vein + elimination of reflux)</td>
<td>At 3 months: 1. 83% 2. 87 / 89% At 1 year: 1. 79% 2. 86 / 76%</td>
</tr>
<tr>
<td></td>
<td>2. Surgery/sclerotherapy</td>
<td>94/125</td>
<td></td>
<td></td>
<td>- response to treatment at 1 year</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- median time to resumption of normal activities</td>
<td></td>
</tr>
<tr>
<td>Bountouroglou et al. 2006</td>
<td>1. UGFS + SFJ ligation</td>
<td>29</td>
<td>GSV</td>
<td>3 mo</td>
<td>- median time to return to normal activities and QoL</td>
<td>Median time to return to normal activities 1. 2 days 2. 8 days</td>
</tr>
<tr>
<td></td>
<td>2. surgery</td>
<td>23</td>
<td></td>
<td></td>
<td>- frequency of complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- cost of treatment</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>- (closure rate: full or partial obliteration without reflux)</td>
<td></td>
</tr>
</tbody>
</table>

SFJ, saphenofemoral junction; GSV, great saphenous vein; FU, follow-up; y, years; AVP, ambulatory venous pressure; SSV, small saphenous vein; UGFS, ultrasound-guided foam sclerotherapy; mo, months; QoL, quality of life
Three recent RCTs have compared EVLT with surgery in patients with GSV incompetence (Darwood et al. 2008, Kalteis et al. 2008, Rasmussen et al. 2007). In all these studies, QoL improvement and the technical outcome were similar.

In the RCTs comparing endovenous RFA with surgery, RFA was superior to surgery in its impact on QoL and time to return to preoperative level of activity (Lurie et al. 2003, 2005), and caused less postoperative pain (Hinchliffe et al. 2006, Rautio et al. 2002b). In all these studies, the efficiency of the techniques in eliminating reflux was similar.

A recent meta-analysis reviewed the available studies on the surgical and new therapies and compared the effectiveness of these methods (van den Bos et al. 2009). The inclusion criteria included RCTs, clinical trials, and prospective and retrospective case series on the treatment of truncal varicose veins by surgical stripping (GSV or SSV), EVLT (with all wavelengths), UGFS (all concentrations and sclerosants) and RFA with ultrasound examination as the outcome measure. The technical endpoint was obliteration or complete removal of the insufficient vein. The estimated pooled success rates at 3 years for stripping, EVLT, UGFS, and RFA were about 78%, 94%, 77%, and 84%. After follow-up adjustment, UGFS and RFA were as effective as stripping, whereas EVLT was more effective than any other treatment. The authors concluded that the minimally invasive techniques appear to be at least as effective as surgery (van den Bos et al. 2009).

7.5 Thrombolysis in prevention of the post-thrombotic syndrome

The goals of the treatment of deep venous thrombosis are to prevent the extension or recurrence of DVT and fatal pulmonary embolism, and to minimize the early and late complications (Hull et al. 2001). Although standard anticoagulation therapy with low-molecular weight heparin and warfarin usually prevents recurrence of DVT and PE, it is inadequate treatment for restoration and preservation of venous valve function (Meissner et al. 2007c). Akesson et al. (1990) have demonstrated that most patients with iliofemoral DVT treated with anticoagulation alone have valve incompetence after 5 years.

According to a Cochrane review, early thrombus removal or resolution after the onset of acute DVT improves long-term clinical outcomes (Watson et al. 2004). In two experimental studies using animal models, thrombolysis preserved endothelial function and valve competence (Cho et al. 1998, Rhodes et al. 2000). However, patients receiving thrombolysis have significantly more bleeding complications (Watson et al. 2004). Treatment strategies of thrombus removal include systemic thrombolysis, catheter-directed thrombolysis (CDT), venous thrombectomy, and pharmacomechanical thrombolysis (Comerota et al. 2007a).

A recent Cochrane review assessed the effectiveness of vena caval filters in preventing pulmonary embolism (Young et al. 2007). These metal alloy devices trap the emboli from the deep leg veins. Traditionally, the indications for the placement of an inferior vena cava filter in case of DVT have included contraindication to anticoagulation and complication or failure of anticoagulation therapy (Greenfield et al. 2001). However, permanent filters may lead to increased risk for lower limb DVT, and evidence of their effectiveness is insufficient for any recommendations (Young et al. 2007).
7.5.1 Systemic thrombolysis

In systemic thrombolysis, the thrombolytic agent, usually streptokinase, urokinase or recombinant tissue plasminogen activator (rt-PA), is infused intravenously. In a review of 13 studies comparing systemic thrombolysis and anticoagulation in 591 patients after iliofemoral DVT, the proportion of patients achieving significant or complete lysis was 45% vs. 4%, and the proportion of failed lysis 37% vs. 82% (Comerota et al. 2007a). In the studies that reported the rate of bleeding complications, the incidence of major bleeding was almost four times as high in patients receiving thrombolysis (26% vs. 7.2%). Three patients, one in the heparin and two in the streptokinase group, died of intracranial hemorrhage (Comerota et al. 2007a).

7.5.2 Catheter-directed thrombolysis

In catheter-directed thrombolysis, the thrombolytic agent is administered directly into the thrombus (Comerota 2001). This treatment is often combined with balloon angioplasty, stenting, or thrombectomy (Alesh et al. 2007).

Numerous prospective and retrospective reports have demonstrated favorable outcomes of CDT (Comerota et al. 2007b). Bjarnason et al. (1997) reported the outcome of CDT in 77 patients with 87 limbs with iliofemoral DVT. The overall success rate was 79%, and the rate of major bleeds 5%, and of PE 1%. In a National Multicenter Registry of 287 patients with 303 limbs with iliofemoral or femoro-popliteal DVT, the rate of complete or partial (50 to 99%) lysis was 83%, and the thrombus-free survival at 6 months 65% and at 12 months 60% (Mewissen et al. 1999). Patients with acute, first-time iliofemoral DVT had the highest patency at one year: 96%. In this study, early success correlated directly with valve function at 6 months: the rate of valvular competence in patients with <50% thrombolysis was 38%, and in patients with complete lysis 72%. The rate of major bleeds in this study was 11% including three patients with intracranial bleeding, and the rate of PE 1% (Mewissen et al. 1999). Sillesen et al. and Protack et al. retrospectively analyzed patients who had undergone CDT for DVT. In the Sillesen et al. study (2005), the initial success rate was 93% (42 of 45), and after an average of 24 months’ follow-up, no recurrent thrombosis among the 42 patients with open veins occurred. Protack et al. (2007) demonstrated technical success in 63%, and the freedom from recurrent DVT at one, two, and three years in 83%, 83%, and 75%.

Alesh et al. (2007) evaluated the effectiveness of CDT and compared the results with the results of RCTs of systemic thrombolysis in a systematic review. In this review, the rates of complete early recanalization of occluded veins were higher with catheter-directed thrombolysis alone, 90%, or followed by adjunct therapy, 76%, than with systemic thrombolysis, 28%. The prevalence of PTS was also lower after catheter-directed combined with adjunct therapy than after systemic thrombolysis, 27% vs. 57%. The rates of any bleeding (usually minor) were higher with catheter-directed than with systemic thrombolysis, 30% vs. 16%. The author of the review reminded us that the methods of the studies were heterogeneous, and results should be interpreted with caution (Alesh et al. 2007). Comerota et al. (2000) compared a cohort of patients in the National Multicenter
Registry to patients with iliofemoral DVT treated with anticoagulation alone in the same institution. All patients filled in a QoL questionnaire at 16 and 22 months post treatment. Patients treated with CDT reported better overall physical functioning, less stigma, less health distress, and fewer post-thrombotic symptoms. QoL results were directly related to initial success of thrombolysis.

Elsharawy et al. (2002) have compared CDT and anticoagulation in a small prospective randomized trial with 6 months’ follow-up and demonstrated that after thrombolysis, the rate of patent veins was higher (72% vs. 12%) and the rate of venous reflux lower (11% vs. 41%). One patient developed PE in the anticoagulation group; no major bleeds occurred.

Short-term results of the first multi-center, prospective, randomized controlled trial comparing CDT and anticoagulation therapy alone in patients with first-time objectively verified iliofemoral DVT have recently become available (Enden et al. 2009) (Table 12). Iliofemoral patency at 6 months was significantly increased and, venous obstruction, but not insufficiency, reduced. This study is ongoing and will provide data on long-term functional efficacy of CDT in terms of prevalence of PTS at 2 years (Enden et al. 2007).

7.5.3 Venous thrombectomy

Venous thrombectomy has improved the early and long-term results of extensive DVT (Comerota et al. 2007b). Comerota et al. (2006) reported the technical details. Plate et al. (1997) reported 10-year results of thrombectomy for iliofemoral DVT. In that RCT, patients randomized to thrombectomy demonstrated improved patency, lower venous pressures, less edema, and fewer post-thrombotic symptoms than did patients who had received anticoagulation.

Blättler at al. (2004) combined surgical thrombectomy of the iliofemoral venous system and regional thrombolysis with a thigh tourniquet to aid removal of the distal
thrombi. In that report, all 33 patients had patent veins with no recurrence or clinical signs of post-thrombotic symptoms at one year follow-up.

7.5.4 Pharmacomechanical thrombolysis

Pharmacomechanical thrombolysis combines catheter-directed thrombolysis with adjunctive mechanical methods in treatment of extensive venous thrombosis (Cynamon et al. 2006, Lee et al. 2006, Vedantham et al. 2004). Several percutaneous mechanical thrombectomy devices exist, the newest one being the Trellis® catheter (Comerota et al. 2007b). This hybrid catheter isolates the thrombosed vein segment between two occluding balloons. The method includes infusion of the plasminogen activator into the thrombus between the balloons and aspiration of the liquefied and particulate thrombus. The advantages of this method are rapid resolution of the thrombus, avoidance of systemic thrombolysis by reduction of exposure to plasminogen activator, and prevention of PE by proximal balloon occlusion (Comerota et al. 2007b). Hilleman et al. (2008) summarized the preliminary experience with the Trellis-8 infusion catheter (TIC) in the treatment of DVT and compared the outcome to that with CDT by meta-analysis. Complete and partial (50-99%) lysis was more common in patients treated with TIC than in those treated with CDT: 93% vs. 79%. The rate of major hemorrhage was significantly lower: nil vs. 8.5%.

7.6 Deep venous reconstructions

The rationale for deep venous reconstructions is the same as for superficial venous surgery: to eliminate venous reflux and to correct any pathological venous hemodynamics. Surgical correction of deep venous reflux has been under development for the past 30 years; Kistner first reported a method of internal valvuloplasty for primary deep venous incompetence (DVI) in 1968. At present, however, evidence is still insufficient to recommend any form of valvuloplasty or other surgical procedure for treatment of DVI (Hardy et al. 2004). Thus, compression therapy remains the treatment of choice for most patients.

7.6.1 Indications and planning

Before considering deep venous reconstruction, all patients with documented DVI should receive optimal conservative treatment and preferably undergo superficial or perforating vein surgery or both, if incompetence in two or all three venous systems coexists. Only patients who have persistent, severe manifestations of CVI, most often active or healed ulcer and occasionally patients with other disabling symptoms are candidates for surgical correction of the deep venous system. In addition, patients should be motivated and compliant with post-operative management (Nachreiner et al. 2001, O'Donnell 2001).

Prior to the operation, all patients should undergo a complete history and clinical examination, duplex scanning, and hemodynamic testing such as air plethysmography, as
well as ascending and descending phlebography. The purposes are to assess the severity and anatomic extent of the disease, and to differentiate reflux from obstruction, as well as to distinguish primary from post-thrombotic disease (Nachreiner et al. 2001, O'Donnell 2001). Moreover, both proximal primary reflux and distal PTS may be present in the same leg (Masuda et al. 1994b). All patients with PTS should undergo screening for hypercoagulable state.

7.6.2 Surgical procedures

**Internal valvuloplasty**

Internal valvuloplasty is the original operation for primary DVI. In this technique, tightening the floppy valve leaflets by plicating the redundant valve cusp to the vein wall restores competence (Nachreiner et al. 2001). Techniques for gaining valve exposure include longitudinal venotomy through the valve commissure (Kistner 1968), a supracomissural approach (Raju 1983), and T-shaped venotomy (Sottiurai 1988), as well as the newest technique called the “Trapdoor” internal valvuloplasty (Tripathi et al. 2001). To avoid thrombosis, anticoagulation with heparin prior to valve repair is important. Postoperative care includes long-term anticoagulation, leg elevation while resting, and compression stockings (Nachreiner et al. 2001).

When treating primary reflux, valvuloplasty of the most proximal valve of the femoral vein is usually sufficient, if the deep femoral vein (DFV) is competent (Cheatle et al. 1994). Otherwise, repair of more than one valve may be preferable, as several authors have documented persistent DFV reflux as resulting in poor clinical and hemodynamic outcome (Eriksson et al. 1986, Masuda et al. 1994b).

**External valvuloplasty**

In 1990, Kistner reported the new technique of external valvuloplasty, which does not require an open venotomy, as the sutures are placed from outside to narrow the commissure and to reduce the vein diameter. The advantages are less venous trauma, shorter operative times, and continuous blood flow during the operation. Thus, perioperative anticoagulation is not mandatory. The disadvantage is the lack of direct visualization (Nachreiner et al. 2001).

Several authors have modified this technique: Gloviczki et al. (1991) introduced angioscopic-assisted valvuloplasty, Belcaro et al. (1993) limited anterior plication, and Raju et al. (2000a) transcommissural valvuloplasty. Earlier, Hallberg (1972) had described a simpler method of repair by external wrapping, which Raju and Fredericks (1988) employed clinically. They covered the valve site of a vein which had gone into spasm with surgical handling and become competent with an external synthetic support. Later, de Souza et al. (2001) combined the closed technique of external valvuloplasty with the Dacron sleeve technique.
Vein transposition and valve transplantation

Deep venous thrombosis causes variable valve damage, but in some patients, the valve anatomy may be sufficiently preserved to allow direct repair by techniques used for correcting primary valvular incompetence (Raju et al. 2000b). If the valve has been damaged beyond repair, however, a direct technique is not feasible. Indirect techniques include vein transposition and venous valve transplantation, which are complex procedures and thus require careful patient selection and also perioperative heparinization (O'Donnell 2001).

Kistner (1979) described a vein transposition technique for patients with a competent saphenous or deep femoral valve and deep venous reflux due to PTS. The purpose is to transpose a competent venous segment, most commonly ipsilateral GSV, into the main deep venous system at groin level by ligating the deep vein and connecting it to GSV below competent preterminal valve (O'Donnell 2001).

Taheri et al. (1982) introduced brachial valve, and Raju et al. (1981) axillary valve transplantation. Taheri inserted a segment of the brachial vein, and Raju a segment of the axillary vein into the femoral vein (FV). In addition, Raju enclosed the donor segment in a Dacron sleeve. Because 30 to 40% of axillary vein valves are incompetent, it is important to check the valve function with a strip test and repair the incompetent valve before transplantation (Raju et al. 1988). Both Taheri and Raju observed progressive dilation of the transplanted segment and deterioration of the valvular function, which were thought to be due to a size mismatch between the donor and the FV (Raju et al. 1988; Taheri et al. 1985). To provide a better size-match, O’Donnell (1987) introduced a new approach: he transplanted a segment of the axillary vein into the above-knee popliteal vein. Another advantage of this technique is restoration of a functioning valve in the popliteal vein, which would play a gatekeeper role above the calf muscle pump.

Puggioni et al. (2004) has described surgical disobliteration—endophlebectomy—of post-thrombotic deep veins. This technique consists of removal of the synechiae attached to the intimal layer of chronically obstructed venous segments during various kinds of deep venous reconstructions. The purpose is to relieve obstruction and to increase inflow and outflow surrounding the reconstruction.

New techniques

Several authors have described new techniques for the treatment of deep venous reflux, most of which aim to find valve substitutes for those patients without autogenous valves. Many experimental attempts have been unsuccessful (Sheridan et al. 2005). Dalsing et al. published in 1999 a feasibility study in patients with chronic deep venous insufficiency to determine whether cryopreserved venous valve allografts would remain patent. Although the short-term patency and competency were reasonable, Neglén and Raju (2003) later demonstrated that reflux repair with cryovalves in patients with PTS caused high morbidity and had poor midterm competency and clinical results. Plagnol et al. (1999) developed an autogenous valve reconstruction technique for post-thrombotic reflux. This
technique involves creation of a new valve using a segment from the proximal end of the GSV and invaginations of this segment into the incompetent deep vein.

7.6.3 Complications

Deep venous reconstructive surgery is a relatively safe procedure, and complications related to this operation are characteristic of any surgical procedure and include hematoma formation, wound infection, lymphatic leak, and deep venous thrombosis (Nachreiner et al. 2001, O'Donnell 2001). Based on case series, the rate of hematomas has been 2 to 11%, the rate of wound infections 2 to 4%, and the rate of seroma formation 2 to 4%. Widespread deep venous thrombosis has been rare, occurring in 0 to 11% (Nachreiner et al. 2001). The rate of surgical site thrombosis appears to be higher following vein transposition than following vein valve transplantation: 9.6% (O'Donnell 2001).

7.6.4 Outcome

Published evidence regarding the short- and long-term efficacy of deep venous reconstructions consists mainly of case series (Scott et al. 2004). A recent Cochrane review on surgery for deep venous incompetence included only three RCTs, none of which evaluated results for surgery on PTS (Hardy et al. 2004). Non-randomized comparative studies often have many confounding factors such as uneven sample sizes, heterogenous patient populations, and thus few common outcomes. In many studies, attributing any beneficial outcome to deep venous reconstruction is impossible, because of applied adjunctive superficial venous surgery (Scott et al. 2004).

The outcome measures of reconstructions include competency or durability, patency of the reconstructed segments, ulcer healing and recurrence, and overall clinical success, as well as changes in venous refilling time and ambulatory venous pressure (Hardy et al. 2004). The outcomes of differing surgical procedures vary, as does the outcome of reconstructions for primary and post-thrombotic deep venous incompetence (Sheridan et al. 2005).

Internal valvuloplasty

The average rate of valve competency one to 252 months after internal valve repair in several clinical series has been approximately 70% (Nachreiner et al. 2001, Sheridan et al. 2005). Freedom from ulcer recurrence and the rate of reduction of pain to mild levels after 6 to 252 months of follow-up have been 60 to 80% (Nachreiner et al. 2001). Patients with good clinical outcome usually have a fully competent or mildly incompetent valve at the site of repair, whereas those with recurrence of symptoms suffer reflux (Kistner et al. 1995). The reported average rate of symptom recurrence or an unchanged clinical situation has been approximately 22% (Sheridan et al. 2005). Kistner et al. have followed their patients requiring internal valvuloplasty from 1968. The 10-year cumulative clinical
success rate was 73% (Masuda et al. 1994b). The average rate of achieving some hemodynamic improvement, as determined by plethysmography or AVP measurements, has been 74% (Sheridan et al. 2005). However, postoperative venous pressures fail to correlate well with the clinical result (Kistner et al. 1995).

Makarova et al. (2001) have studied the effect of internal valvuloplasty of the femoral vein on the course of primary CVI in patients with combined deep and superficial venous reflux in a prospective, randomized fashion. The authors compared the outcome of superficial venous surgery alone to that of an additional internal valvuloplasty 7 to 8 years after the operation. Before the operation, they followed the patients for 5 years to determine whether the disease was progressive or stable, and then randomly assigned them to treatment groups. Outcome depended on the type of clinical dynamics: Patients with progressive disease had a significantly higher rate of improvement in their clinical condition in the study group (valvuloplasty + superficial venous surgery), whereas the results in patients with stable disease were similar between the groups. The rate of competency of the repaired valves was approximately 70% (Makarova et al. 2001).

**External valvuloplasty**

The results of external valvuloplasty with Kistner’s technique seem to be inferior to those after internal valve repair (Raju et al. 1996, Tripathi et al. 2004). Tripathi et al. performed deep venous valve reconstructions for non-healing leg ulcers and reported competency at the repaired valve site 2 years after external valvuloplasty in 31%, and ulcer healing in 50%.

The results after angioscopic-assisted valvuloplasty appear to be more promising in patients with combined primary deep and superficial venous incompetence (Sakuda et al. 2002). In this prospective, non-randomized study comparing angioscopic-assisted external valvuloplasty of the femoral vein and superficial venous surgery with superficial surgery alone, competency was maintained 2 years after valvuloplasty in 94%, and venous filling index improved. In addition, patients who had undergone valvuloplasty had lower postoperative venous index values as well as lower clinical severity and disability scores.

Belgaro and Wang have studied the effect of external valvuloplasty in the treatment of moderate, primary combined deep, and superficial venous insufficiency in a randomized fashion (Belcaro et al. 1999; Wang et al. 2006). Belcaro (1999) studied the effect of external valvuloplasty of the femoral vein with limited anterior plication (LAP) by randomizing patients to superficial venous surgery alone (18 patients completed the study) or to superficial surgery and LAP (17 patients completed). After 10 years of follow-up, all repaired femoral vein valves were competent, and patients in the LAP group had significantly lower AVP, a longer refilling time and a better QoL. The authors thus concluded that LAP may be an alternative to external valvuloplasty in selected patients with functional cusps and incompetence due to relative enlargement of the femoral vein. Wang et al. (2006) treated 40 patients with bilateral disease with their modification of external valvuloplasty and superficial venous surgery or with superficial surgery alone. One limb of each patient was randomized into either operation, with the other limb serving as the control. The rate of valve competency 3 years after the operation was about 91%. 52
Compared to limbs with superficial surgery alone, limbs with a repaired valve had less venous reflux, better reflux indices, lower severity scores, and better muscle pump function.

Raju et al. (2000a) have reported results after transcommissural valvuloplasty in patients with either primary or secondary DVI: The rate of valve competency 42 months after this operation was 79%, the cumulative competency rate at 30 months was 59%, and cumulative ulcer-recurrence-free rate 63%. No difference in any of the outcome measures between primary and post-thrombotic valves was observable. In this study, the most frequent site of valve repair was the femoral vein; the other repaired valve sites were the common and deep femoral vein, the popliteal vein, and the posterior tibial vein. A number of patients had multiple sites repaired (Raju et al. 2000a). Rosales et al. (2006) have used the same transcommissural technique in patients with primary CVI. In this small series, the rate of competency at 3 years was 64%, and at 5 years 52% and the rate of ulcer healing 57%, and it seemed that multiple valve repairs at the same level (multistation repairs) yielded the longest durability.

Us et al. (2007) recently published a retrospective study demonstrating that external banding with a Dacron sleeve extends the durability of external valvuloplasty. This study included patients with primary combined deep and superficial venous incompetence treated with ankle-to-groin stripping of the GSV and transcommissural external valve repair of the common femoral vein with or without external banding. The durability of the repairs without banding decreased during follow-up from 85% at 6 months to 48.5% at 60 months. The rate of competency of the repairs with banding decreased significantly less: from 88% to 69%. The rate of ulcer healing at 4 years was also higher in patients with externally supported valve repair: 72% vs. 92% (Us et al. 2007).

**Vein transposition and valve transplantation**

Overall, long-term outcome of reconstructions for post-thrombotic syndrome is inferior to that for primary valve incompetence (Masuda et al. 1994b, Raju et al. 1996, Tripathi et al. 2004). The average rate of competency of valve transposition after 3 to 256 months of follow-up is 58% and the percentage of patients with good results 5 years after the surgery 40 to 50% (Sheridan et al. 2005). Perrin (2000) has reported a 5-year cumulative ulcer-free interval of 75%. The ulcer recurrence rate in clinical series can be 35% (O'Donnell 2001).

Severe limitations in reporting standards in studies evaluating the outcome of valve transplantations hamper analysis of the results (O'Donnell 2001). In addition, it is difficult in some studies to separate the results for transplantation from those of the other procedures (Masuda et al. 1994b). Overall, the average rate of competency of valve transplantation in several clinical series with 3 to 156 months of follow-up is approximately 52% (Perrin 2000, Sheridan et al. 2005, Tripathi et al. 2004). The average rate of patency has been high, approximately 84%, recurrence of symptoms or unchanged clinical situation 33%, and hemodynamic improvement 76% (Sheridan et al. 2005). The average rate of initial ulcer healing has been 79% (O'Donnell 2001). The ulcer-free interval at 6 years in studies with follow-up data beyond 5 years has been 50 to 65% (Bry et al. 1995, Perrin 2000, Raju et al. 1999).
In a recent study by Rosales et al. (2008), 32 selected patients with secondary CVI underwent various venous valve reconstructions (external valve repair, transposition, and transplantation), which resulted in valvular competence and a clinical success rate of 47% and 40% at 3 and 7 years. Clinical success lasted longer in patients with AVP reduction than for those without hemodynamic improvement. A significant factor associated with improved AVP was popliteal vein reconstruction.

In conclusion, most patients with primary DVI seem to benefit from valve repair, whereas operations for post-thrombotic syndrome are less successful. Scientific evidence on surgical treatment of DVI is insufficient, and until large randomized-controlled trials with long-term follow-up are available, conservative therapy will remain the principal mode of treatment.
Aims of the study

The main purpose of this study was to evaluate treatment using duplex-derived reflux assessment as the outcome measure in patients with axial superficial or deep venous incompetence or deep venous thrombosis.

The specific aims of the five separate projects were to evaluate:

1. comparison of the ability of two surgical services to abolish superficial venous reflux and to evaluate the role of preoperative duplex examination and marking of axial venous reflux.

2. how doppler-derived information can be communicated in written form to the surgeon before superficial venous surgery, and whether the surgery is adequate without preoperative venous marking.

3. the short-term efficacy and safety of ultrasound-guided foam sclerotherapy in the early stages of the learning curve in patients with axial superficial venous incompetence.

4. venous reflux and the obstruction pattern after catheter-directed and systemic thrombolysis of deep iliofemoral venous thrombosis.

5. the long-term durability and clinical success of various deep venous reconstruction techniques for severe chronic venous insufficiency.
Patients and methods

Data source

Data from Helsinki University Central Hospital (HUCH), Hyvinkää Hospital and Laseri Hospital were retrieved from patient records. All studies were retrospective and included a cross-sectional follow-up evaluation. The Ethics Committee of HUCH approved all the studies, and each participating patient signed a written consent.

Patients and study designs

Study I: Service comparison between vascular and general surgery

The study included 55 patients who had undergone superficial venous surgery based on either preoperative duplex evaluation and doppler marking (vascular surgical service, VSS) or clinical findings (general surgical service, GSS) (Table 13). The operations were performed at HUCH (VSS) or at Hyvinkää Hospital (GSS) during 1997-2000 (Table 14).

Study II: Communicating doppler-derived information in superficial venous surgery

The study comprised 78 patients with 102 limbs which had been operated on for superficial venous insufficiency in 2001. All patients had undergone a preoperative doppler (~59% of the limbs) or duplex (~41%) evaluation at the outpatient clinic of the Department of Vascular Surgery at HUCH. The severity of the disease was graded with clinical (C) classification and venous clinical severity (VCSS) and disability scores. General or vascular surgeons performed half of the operations in two private hospitals according to a written plan sent to the surgical units. Vascular surgeons or trainees operated on the other half at hospitals affiliated with the university unit, and just prior to the procedure performed preoperative venous marking with doppler (Table 14). The patients were matched by age, gender, C class, and operative status (primary or reoperation) to create two comparable groups (preoperative doppler marking or no preoperative doppler marking) (Table 13).

At the follow-up visit, disease severity was again graded with VCSS, C classification, and disability scores. The patients also filled in the Aberdeen and 15D (QoL) questionnaires. Analysis of the duplex results included comparison of the elimination of known reflux (complete, partial or failed) and comparison of the postoperative reflux at preoperatively identified reflux sites as well as at all detectable axial reflux sites (including sites not identified in the preoperative evaluation).
Table 13. Patient characteristics in Studies I, II, III, and V of treatment of venous reflux

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VSS</td>
<td>GSS</td>
<td>Preoperative doppler marking</td>
<td>No preoperative doppler marking</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>27</td>
<td>39</td>
<td>39</td>
<td>112</td>
</tr>
<tr>
<td>Number of males</td>
<td>12</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Number of limbs</td>
<td>33</td>
<td>35</td>
<td>51</td>
<td>51</td>
<td>152</td>
</tr>
<tr>
<td>Age (range)</td>
<td>56.1 (24-91)</td>
<td>56.1 (38-76)</td>
<td>47.1 (24-69)</td>
<td>52 (27-80)</td>
<td>50 (29-75)</td>
</tr>
<tr>
<td>Clinical class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2-4</td>
<td>20</td>
<td>35</td>
<td>51</td>
<td>51</td>
<td>151</td>
</tr>
<tr>
<td>C5</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C6</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary</td>
<td>23</td>
<td>35</td>
<td>50</td>
<td>48</td>
<td>152</td>
</tr>
<tr>
<td>Secondary</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Previous superficial venous surgery</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>16</td>
<td>59</td>
</tr>
<tr>
<td>Follow-up time in months (range)</td>
<td>38 (24-60)</td>
<td>41 (24-60)</td>
<td>24</td>
<td>18-24</td>
<td>10 (5.5-16.5)</td>
</tr>
</tbody>
</table>

VSS, vascular surgical service; GSS, general surgical service

Study III: Outcome of ultrasound-guided foam sclerotherapy

The study comprised 112 patients who had undergone ultrasound-guided foam sclerotherapy for a total of 167 incompetent superficial veins (139 great and 28 small saphenous veins) between November 2004 and August 2005 as the first patients at Laseri Hospital in Helsinki (Table 13). Of the 167 veins treated, 138 (83%) had primary (GSV 94, anterior or dorsal branch 16, SSV 28) and 29 recurrent reflux (21 recurrent GSVs, 8 anterior branches). The patients underwent the first duplex evaluation usually 2 to 6 weeks after the treatment session. At the follow-up visits, the surgeon examined the treated segments with duplex and if the vein was not occluded performed re-treatment.

The duplex findings at the final follow-up evaluation 5.5 to 16.5 months after the last treatment session that achieved occlusion of the treated vein were classified according to the efficacy criteria for UGFS set by the second consensus committee meeting on foam sclerotherapy (Breu et al. 2008): 2a, complete disappearance of the treated vein or fibrous
Table 14. Number of surgical procedures in Studies I and II

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>I</th>
<th>II</th>
<th>Preoperative doppler marking</th>
<th>No preoperative doppler marking</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFJ ligation without GSV</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>GSV stripping</td>
<td>18</td>
<td>20</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>SFJ ligation + GSV stripping</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>GSV stripping without SFJ ligation</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SFJ ligation + GSV + SSV stripping</td>
<td>5</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Calf GSV stripping only</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SSV stripping alone</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Multiple avulsions or perforating vein ligation only</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Deep venous reconstruction</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

VSS, vascular surgical service; GSS, general surgical service; SFJ, sapheno-femoral junction; GSV, great saphenous vein; SSV, small saphenous vein.

cord; 2b, complete occlusion of the treated vein segment; 2c, patency of the treated vein segment and antegrade flow; 1, reflux ≤1s, partial incompressibility and partial occlusion of the treated vein segment, and 0, reflux >1s, complete (or incomplete) patency. In the final analysis, 2a and 2b were combined (2a=2a+2b), because the type-2b result was rare. The overall treatment result was further classified by combining the clinical and duplex data into three categories: 2, complete success; 1, partial success; 0, no success. Criteria for complete success were: 2a, 2b or 2c result on duplex, clinical picture normalized and symptoms absent or improved; partial success: reflux ≤1 second, partial incompressibility or occlusion of the treated vein segment, clinical picture normalized or improved and symptoms absent or improved; no success: reflux >1 second or unchanged, complete (or incomplete) patency, clinical picture and symptoms unchanged or worsened.

Study IV: Comparison of reflux pattern after catheter-directed and systemic thrombolysis

The study comprised 32 patients who had suffered from unilateral deep iliofemoral venous thrombosis from July 1999 to June 2000, and had received either systemic or catheter-directed thrombolysis in addition with low molecular weight-heparin and oral anticoagulants at HUCH (Table 15). All patients filled in a venous patient questionnaire as
Table 15. Patient characteristics in Study IV on thrombolysis of deep venous thrombosis

<table>
<thead>
<tr>
<th>Groups</th>
<th>Catheter-directed thrombolysis</th>
<th>Systemic thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Number of males</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Age (range)</td>
<td>56 (21-86)</td>
<td>61 (35-81)</td>
</tr>
<tr>
<td>Thrombolytic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alteplase (n)</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Streptokinase (n)</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>2-3</td>
<td>2-3</td>
</tr>
</tbody>
</table>

well as a questionnaire concerning risk factors and duration of anticoagulation therapy.

**Study V: Outcome of deep venous reconstruction**

During 1996-2000, a total of 43 patients underwent a deep venous reconstruction for severe deep venous incompetence at HUCH. Follow-up visits were at one month, six months, and annually thereafter with extra admissions at need. Four of those patients did not participate in the final follow-up evaluation, and their data are included in the life-table analysis only for durability of the reconstructions. One patient was omitted due to lack of follow-up data. Thus, 38 patients formed the study group (Table 13). Primary reconstructions included 12 internal and 7 external valvuloplasties, 14 vein transpositions, and 33 valve transplantations (including those four patients with no final follow-up visit data). Half the patients underwent two or three separate repairs at the same operation. A total of 30 patients also underwent a superficial venous surgery before the reconstruction. During the follow-up, 15 patients needed a reoperation, six of which were deep venous reconstructions.

Preoperative clinical evaluation included a detailed case history and physical examination, as well as CEAP classification, and venous clinical severity and disability scoring, which were repeated at the final follow-up visit to assess any possible changes in clinical status. The preoperative imaging studies included duplex scanning as well as ascending and descending functional cine phlebography. The follow-up duplex evaluations assessed the reconstructed segments and valves. Severe reflux (>2 s) on duplex at a repaired site indicated a failure. Primary durability was the time when all reconstructions were competent. Criteria for clinical success were as follows: no symptoms or only mild pain, swelling or skin changes, and ability to work with or without compression stockings. Freedom from ulceration was the percentage of ulcer patients who did not have ulcer recurrence during the follow-up.
PATIENTS AND METHODS

**Duplex ultrasound examination**

All follow-up evaluations included a duplex ultrasound examination of the lower extremities performed by one or two independent examiners not involved with treatment. The follow-up evaluations for Studies I, II, IV, and V were performed at the outpatient clinic of the Department of Vascular Surgery at HUCH with a Hewlett Packard M2410A scanner (USA) using a 5 MHz probe. The ultrasound scanning was performed in a standing position with patients’ weight mainly on the contralateral leg. The groin, the thigh, and the calf were examined for superficial, perforator, and deep venous reflux. Reflux was provoked with the release of a distal pneumatic cuff in a standardized fashion (Venopulse venous compression unit, STR Teknikk, Norway). Reflux was considered pathological if it lasted over 0.5 to 1 second (Studies I, II, IV) and severely pathological if it lasted over 2 seconds (Study V).

The duplex scanning for Study III was performed at Laseri Hospital with Aloka alpha 5 and high frequency (5-12 MHz) linear array transducers. Blood movement was created by outflow compression of the thigh and calf muscles, and at the sapheno-femoral junction and in the femoral veins at the groin level, by the Valsalva maneuver. Venous flow was observed after release of the provocation, with a prolonged reflux beyond one second regarded as a sign of valvular incompetence. The function of the deep veins was examined at the groin level and in the popliteal vein.

**Statistical analysis**

Comparisons of the categorical data were analyzed with the chi-square test or Fisher’s exact test (Studies I, II, IV). P-values lower than 0.05 were considered significant. The survival curves were calculated with the Kaplan-Meier life-table analysis method using SPSS (Statistical Package in the Social Sciences) statistical software (Study V).
Results

Study I: Service comparison between vascular and general surgery

Postoperative clinical outcome was not as good in the VSS as in the GSS (Table 16). The proportion of superficial or perforating veins with retrograde flow in both groups was about 40%. However, axial reflux at sapheno-femoral or thigh level was more frequent in the GSS than in the VSS (4 of 33 versus 14 of 35, p=0.009) (Table 17).

Table 16. Clinical outcome and postoperative quality of life in patients operated on for superficial venous incompetence (Studies I and II)

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>VSS n=33 (postop.) GSS n=35 (postop.)</td>
<td>Preoperative doppler marking n=39/51 (patients/limbs) No preoperative doppler marking n=39/51 (patients/limbs)</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>C class, limbs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>VCSS (mean)</td>
<td>5.85</td>
<td>3.43</td>
</tr>
<tr>
<td>Aberdeen, mean (median)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>15D, mean (median)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

VSS, vascular surgical service; GSS, general surgical service; C class, clinical class; VCSS, venous clinical severity score; NA, not available

Study II: Communicating doppler-derived information in superficial venous surgery

In both groups, clinical class, VCSS, and disability score improved equally, and no difference appeared in postoperative quality of life status (Table 16).
RESULTS

Table 17.  Number of limbs with reflux in superficial and perforating veins in patients operated on for superficial venous incompetence (Studies I and II)

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>VSS (postop.)</th>
<th>GSS (postop.)</th>
<th>Preoperative doppler marking</th>
<th>No preoperative doppler marking</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFJ</td>
<td>0</td>
<td>2</td>
<td>NS</td>
<td>30</td>
<td>1 (3.3 %)</td>
<td>24</td>
</tr>
<tr>
<td>Thigh GSV</td>
<td>4</td>
<td>6</td>
<td>NS</td>
<td>38</td>
<td>3 (7.9 %)</td>
<td>34</td>
</tr>
<tr>
<td>Calf GSV</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>21</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Ankle GSV</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Anterior branch of GSV</td>
<td>0</td>
<td>6</td>
<td>0.025</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Posterior arch vein</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>15</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>SSV</td>
<td>5</td>
<td>1</td>
<td>NS</td>
<td>13</td>
<td>1 (7.7 %)</td>
<td>12</td>
</tr>
<tr>
<td>Any axial reflux / limb</td>
<td>9</td>
<td>13</td>
<td>NS</td>
<td>48</td>
<td>5 (10 %)</td>
<td>46</td>
</tr>
<tr>
<td>Thigh perforators</td>
<td>3</td>
<td>3</td>
<td>NS</td>
<td>6</td>
<td>2 (33 %)</td>
<td>1</td>
</tr>
<tr>
<td>Calf perforators</td>
<td>6</td>
<td>0</td>
<td>0.010</td>
<td>11</td>
<td>2 (18 %)</td>
<td>2</td>
</tr>
</tbody>
</table>

SFJ, sapheno-femoral junction; GSV, great saphenous vein; SSV, small saphenous vein; NA, not available; NS, non-significant

Overall, the dimensions most affected were sleep and comfort. A common complaint at the follow-up visit was leg pain: 20 patients in the marked group and 17 in the non-marked group reported pain. The number of patients having visible varicose veins was 14 (9 in the marked and 5 in the non-marked group).

Elimination of preoperatively known reflux succeeded better in the marked than in the non-marked group: the proportion of intact refluxing veins (elimination of known reflux failed) in the postoperative evaluation was 2% versus 18% (1 of 51 vs 9 of 51, p=0.008). The differences in preoperatively identified reflux sites were not statistically significant, although residual or recurrent reflux tended to be more frequent in patients with no preoperative doppler marking (Table 17). Any axial reflux (including sites not identified preoperatively) was more common in the non-marked group (11 in the marked versus 21 in the non-marked group, p=0.033). Some venous reflux was present in 41 of 102 (40%) operated limbs, 18 (35%) in the marked and 23 (45%) in the non-marked group.

Studies I and II: Service-related outcome in superficial venous surgery

The VSS group in Study I and the group with preoperative doppler marking in Study II underwent superficial venous surgery at the Department of Vascular Surgery with careful preoperative evaluation with doppler techniques by the operating surgeon. In postoperative evaluation, these patients had fewer reflux sites in the axial superficial thigh.
RESULTS

Figure 3. Proportion of limbs with axial reflux after superficial venous surgery: Comparisons between vascular, general, and private services (unmatched)

Study III: Outcome of ultrasound-guided foam sclerotherapy

Single treatment occluded 150 (90%) veins. Of all the 167 veins treated, 14 required 2, and 3 veins 3 treatment sessions.

The proportion of veins with no reflux after 5.5 to 16.5 months of follow-up was 74% (124 of 167). The treated vein was fibrosed or occluded in 62% and completely patent with reflux in 15% (Table 18). Treatment results in GSV subgroups were similar (Table 18). After successful primary GSV treatment, the sapheno-femoral junction remained open or refluxing in 89% (64 of 72), and after unsuccessful GSV treatment, in 100% (all of 22). The overall treatment result was as follows: complete success 82%, partial success 13%, and no success 5.3%.

Overall, of 112, 104 (93%) patients were satisfied with the treatment. Two reported worsening of symptoms.

The most common complication was hyperpigmentation (Table 19). Of the patients with thrombophlebitis, three required systemic antibiotics. One patient suffered from bilateral DVT and pulmonary embolism; she was hospitalized after the third treatment session and eventually recovered well.
Table 18. Number (percentage) of veins with successful or failed ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Vein</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibrosed/occluded</td>
<td>Patent, no reflux</td>
</tr>
<tr>
<td>GSV</td>
<td>87 (63%)</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>primary GSV</td>
<td>59 (63%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>recurrent GSV</td>
<td>13 (62%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>ant./dorsal branch</td>
<td>15 (65%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>SSV</td>
<td>16 (57%)</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>103 (62%)</td>
<td>21 (13%)</td>
</tr>
</tbody>
</table>

GSV, great saphenous vein; SSV, small saphenous vein

Table 19. Number of complications in 112 patients and 152 limbs treated with ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hyperpigmentation (limbs)</td>
<td>101</td>
</tr>
<tr>
<td>Thrombophlebitis (limbs)</td>
<td>26</td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
</tr>
<tr>
<td>Deep venous thrombosis alone</td>
<td>0</td>
</tr>
<tr>
<td>DVT and pulmonary embolism</td>
<td>1</td>
</tr>
</tbody>
</table>

Study IV: Comparison of reflux pattern after catheter-directed and systemic thrombolysis

No difference existed between the groups as to the length of oral anticoagulation, use of compression stockings, presence of genetic or other risk factors predisposing to deep venous thrombosis. Nor did any difference exist in frequency of major, meaning two (retroperitoneal bleed and large hematoma at the puncture site) in the catheter-directed or one (hematuria) in the systemic-lysis group or minor (four versus six) bleeding complications. Half the patients used compression stockings in the CDT group, and in the systemic thrombolysis group, 38%.

Patients treated with CDT tended to be lower C class (Table 20). Disability scores (Table 20) or the frequency of obstruction (5 in the catheter-directed and 8 in the systemic thrombolysis group) did not differ significantly.

The CDT group had significantly less deep and superficial venous reflux (44% versus 81%, p=0.03; 25% versus 63%, p=0.03) (Fig 4), and a higher proportion of preserved valvular competence (44% versus 13%, p=0.049).
RESULTS

Table 20. Clinical outcome at follow-up after thrombolysis (number of limbs in each category)

<table>
<thead>
<tr>
<th>Clinical class</th>
<th>Catheter-directed thrombolysis (n=16)</th>
<th>Systemic thrombolysis (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>C1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>C2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>C4</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability score</th>
<th>Catheter-directed thrombolysis</th>
<th>Systemic thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 4. Number of limbs with incompetent venous segments after catheter-directed or systemic thrombolysis for deep venous thrombosis

SSV, small saphenous vein; GSV, great saphenous vein; FV, femoral vein; DFV, deep femoral vein; CFV, common femoral vein
**RESULTS**

*Figure 5.* Cumulative clinical success rate after deep venous reconstruction in 9 patients with primary or congenital disease (blue line) and in 29 with secondary disease (green line). Numbers represent total limbs at risk. Censored cases indicated by marks on the lines.

---

**Study V: Outcome of deep venous reconstruction**

The venous clinical severity score improved in 74% of the patients (mean VCSS decreased from 11.8 to 9.5), whereas the disability score decreased in 7, was unaltered in 26, and increased in 5 patients. The cumulative rate of clinical success at 4 years of follow-up was 23%. In patients with primary or congenital disease it was 44%, and in secondary disease 17% (Fig 5).

Of the nine active ulcers at the time of operation, six healed within the first year. Three of these ulcers recurred, and three did not heal during the first post-operative year. Of the 11 patients with a healed ulcer at the time of the operation, five had a recurrence. Freedom from ulceration 4 years after the operation or ulcer healing was 54% (Fig 6).

At the final follow-up visit, only three patients had no reflux detected in superficial, perforating, or deep veins. The proportion of patients with competent or only mildly incompetent reconstruction was 45%. Of 13 primary reconstructions for primary or congenital disease, nine were competent. The cumulative durability rates of different reconstructions at 4 years were as follows: valvuloplasties 55% (external 71%, internal 42%), transpositions 43%, and transplantations 16% (axillary 13%, saphenous 26%) (Fig 7). Of the six re-reconstructions, one remained durable.
RESULTS

**Figure 6.** Cumulative freedom from ulcer after deep venous reconstruction in 20 patients with active or healed ulceration. [Marks on] Horizontal lines represent censored cases, and the numbers total limbs at risk. (Reprinted from Eur J Vasc Endovasc Surg 35, Lehtola A, Oinonen A, Sugano N, Albäck A, Lepäntalo M. Deep venous reconstruction: long-term outcome in patients with primary or post-thrombotic deep venous incompetence, 487-493, 2007, with permission from Elsevier)

**Figure 7.** Cumulative durability rate of different deep venous reconstructions. (Reprinted from Eur J Vasc Endovasc Surg 35, Lehtola A, Oinonen A, Sugano N, Albäck A, Lepäntalo M. Deep venous reconstruction: long-term outcome in patients with primary or post-thrombotic deep venous incompetence, 487-493, 2007, with permission from Elsevier)
DISCUSSION

Discussion

To my own knowledge, this is the first thesis in Finland evaluating the treatment results of various methods aimed at eliminating axial venous reflux. Despite several limitations, the study provides some important results. Treatment of chronic venous disease is challenging and will be unsuccessful without careful diagnostic evaluation, best performed with duplex ultrasound. Several therapeutic options are nowadays available, but the future role of each method in treatment of CVD is unclear. Improving the early treatment results of deep venous thrombosis is worthwhile, because this seems to reduce the development of post-thrombotic syndrome. Treatment of this complication is difficult, and the outcomes of deep venous reconstructions unsatisfactory.

Limitations of the study

Clinical studies are never free from confounding factors limiting interpretation of the results. All the studies included in this thesis are retrospective, which certainly brings several flaws: The patients were examined and treated as part of a normal clinical routine and never in a strictly standardized manner. Data were collected retrospectively from patient files, and the adequacy of the information gathered depended on how precisely the clinician had described the clinical and imaging status. A number of surgeons with varying degrees of experience were involved in the treatment, with no ideal conditions achievable. Some selection bias inevitably has occurred.

The risk for observer bias is a problem related to cohort studies especially, if those treating the patients are also responsible for the outcome examination. Throughout this study, we tried to separate the examiners who performed the cross-sectional follow-up evaluations from those who were involved in the treatment.

In studies evaluating venous surgery, the patient population is often heterogeneous. Exclusions are necessary in any attempt to make the population more homogenous in order to improve internal validity. This reduces sample sizes and limits the scientific value of comparisons between groups and the conclusions of the case series. Different parts of this study have different limitations.

Service comparison between vascular and general surgery

The study design seems outdated by today’s standards. At the time the project was planned, preoperative doppler or duplex examinations were no part of routine diagnostics outside University hospitals. This gave us an opportunity to retrospectively compare treatment results in patients undergoing surgery for superficial venous incompetence with or without preoperative duplex evaluation and doppler marking. However, several factors make interpretation of the results difficult.

First, the baseline characteristics differed considerably. In the VSS group, the proportion of patients with secondary CVD and PTS was 32% and the prevalence of deep
DISCUSSION

venous incompetence at the postoperative evaluation over 60%, whereas all patients in the GSS group had primary CVD, and only 15% had deep venous reflux. Moreover, in the VSS, 46% of the patients had a healed or active ulcer at the time of surgery, but none of the patients in the GSS. Patients with secondary and complicated CVD tend to have more complicated reflux patterns, including more IPVs. Superficial venous surgery is unlikely to correct perforator incompetence in the presence of deep venous reflux (Stuart et al. 1998). This probably explains why refluxing perforators were more common in VSS patients.

Second, even VSS had not achieved a standard routine in duplex evaluation at the time of the study, and the surgeons in the VSS were in different phases of their learning curve. This may lead to underestimation of the value of preoperative duplex examination.

Third, surgeons in the VSS inevitably had more expertise than did those in the GSS, and in particular, handling of the SFJ differed. In the GSS, a number of patients underwent stripping of the GSV without SFJ ligation. This may explain the higher frequency of residual and recurrent axial reflux in the veins of the thigh. Four patients in the VSS underwent deep venous reconstruction. Thus, the results only illustrate the outcome of two different surgical services.

Fourth, surgical outcome was based on the presence of venous reflux only, not on symptoms or recurrence of varicose veins.

Communicating doppler-derived information in superficial venous surgery

All patients in this study underwent their preoperative evaluations at the Department of Vascular Surgery. The surgeons used hand-held doppler in about 60% of the cases. The postoperative evaluation was always performed with duplex. Because HDD is not as accurate as duplex, some reflux sites may have been missed preoperatively.

Vascular surgeons or trainees performed marking of the reflux sites with doppler just before the operation. We have no information about the preoperative evaluation performed in the private hospitals. In principal, the doppler-derived information was sent in written form to the operator, but how these data were used is unclear. Differences in outcomes may perhaps be attributable to differences in surgical techniques, especially regarding treatment of the SFJ, rather than attributable to the lack of preoperative doppler marking.

Because preoperative QoL data are unavailable, the effect of superficial venous surgery on generic or disease-specific QoL is not assessable.

Outcome of ultrasound-guided foam sclerotherapy

This study is a case series with no control group and was conducted at a private hospital, which may affect the patient population seeking treatment. In general, more patients complain about the cosmetic appearance than complain about the complications of venous disease at such hospital than do patients treated in public health care. We excluded patients with small branch varicosities but included those who were asymptomatic but had reflux in a trunk vein.
This study includes four patient groups: those with primary incompetence of a major trunk (GSV or SSV), incompetence of a major tributary, and recurrent varicose veins. Many patients underwent secondary treatments at different time-points. This heterogeneity makes interpretation of the results complicated.

At the time of the first treatments, standardization of the pretreatment duplex examination, and concentrations and amounts of sclerosants, as well as the use of prophylactic anticoagulation was lacking. Diameters of the veins before treatment were available only in 40% of the cases. This made it impossible to draw conclusions from the effect of the diameter.

The outcome of the treatment was sometimes difficult to classify. Many times only part of the vein was fibrosed, and part of it was patent. In those cases, the authors decided together which grade was the most adequate.

It was difficult retrospectively to evaluate the true incidences of thrombophlebitis and hyperpigmentation. At the final follow-up visit, we did not grade the level of hyperpigmentation. Thus, all patients with even a small area of discolored skin were defined as having hyperpigmentation.

**Comparison of reflux pattern after catheter-directed and systemic thrombolysis**

The retrospective patient sampling did not allow detailed analysis of the pre-treatment imaging data, and although the baseline characteristics of the patients appeared comparable, we cannot exclude potential differences in their initial status.

One important confounding factor is the lack of information about earlier thrombotic events, and about the presence of reflux or obstruction before DVT. The postoperative evaluation involved separate analysis of reflux and obstruction, although some patients had combinations of these.

Furthermore, all patients who received CDT underwent post-treatment venography, which allows precise evaluation of the immediate result and of any treatment needed for residual thrombosis, whereas patients who received systemic thrombolysis had venography only if the result of the lysis seemed clinically inadequate.

**Outcome of deep venous reconstruction**

This study is a case series of a highly selected, heterogenous group of patients who have undergone different deep venous reconstructive procedures with simultaneous ablative superficial venous surgery. A number of limitations thus must be borne in mind in interpreting the results.

First, although most patients had secondary CVI, the study also included a few patients with congenital and primary CVI. Between these groups, the clinical picture, the surgical treatment and its outcome, and the prognoses of the disease all differ. Small sample sizes made comparisons between these groups vulnerable to bias.
DISCUSSION

Second, the range of surgical techniques and multiple reconstructions blur conclusions on the efficacy of different reconstructions.

Third, most patients underwent additional superficial venous surgery, which makes it difficult to attribute beneficial outcomes to the deep venous reconstruction. This is a typical problem in most clinical studies evaluating deep venous surgery (Scott et al. 2004). Although ablation of insufficient superficial veins alone may lead to good results in patients with chronic venous ulceration and combined superficial and segmental deep venous incompetence (Adam et al. 2003, Barwell et al. 2004), deep venous reflux in our patients was usually not segmental. Besides, more than half of our patients had undergone a previous superficial venous surgery, which obviously had not succeeded. Our approach, performing deep venous reconstruction and superficial venous surgery simultaneously, was at least partly because of the very limited surgical resources available for treatment of venous disease.

Fourth, during the study period, almost half the patients underwent reoperations—either deep venous reconstructions or superficial venous operations. At the final follow-up visit, it was difficult to separate the effects of the primary reconstructions from those of the reoperations. This issue does not bias the cumulative data as much, however, because reoperation, especially when targeted at the previously repaired site, was usually considered an endpoint.

Fifth, some patients did not attend all scheduled visits. The time-points when an ulcer was considered healed or when it recurred, or when a reconstruction failed, were always just estimates, because sometimes the interval between two follow-up visits was prolonged, making determination of the dates inexact.

Main observations

Service comparison between vascular and general surgery

Despite these limitations, some results are noteworthy. Residual or recurrent reflux was common in both groups, also in patients who had undergone a careful preoperative evaluation with duplex scanning and marking of all reflux sites. Allegra et al. (2007) also demonstrated this finding in a prospective study: The rate of recurrent varicose veins was 25% at 5 years despite preoperative duplex evaluation. Thus, it seems that complete ablation of all reflux sites with surgery is impossible. However, although patients in the VSS had more complicated disease than did patients in the GSS, elimination of axial reflux at thigh level in the VSS group succeeded better. This finding indirectly suggests that prior to ablative superficial venous surgery aiming to eliminate axial venous reflux, careful duplex examination and doppler marking is beneficial. In today’s practice, duplex is a routine method.
Communicating doppler-derived information in superficial venous surgery

Ablative superficial venous surgery was beneficial in both groups in terms of improved venous clinical severity and disability scores. CEAP clinical class improved as well, but for outcome measurements, this 7-point score with relatively static components proved less than useful (Rutherford et al. 2000). Kakkos et al. (2003) showed that VCSS and VDS are sensitive and better for measuring changes in response to superficial venous surgery than is C class in patients with primary varicose veins. He also showed that all these scores improved significantly 6 weeks and 6 months after surgery.

Some reflux was present in 40% of the patients despite careful preoperative evaluation. Study I demonstrated the same result. However, presence of reflux did not always translate to clinical recurrence. Although 40% had some reflux, only 14% had visible varicose veins. And patients in the non-marked group had fewer varicosities despite more widespread reflux in axial veins and more reflux sites in total. Chiesa et al. (2007) demonstrated a correlation between patterns of valve incompetence and clinical features. In that large survey, the frequency of reflux increased along with severity of visible signs of venous disease. However, reflux was rather common also in patients in clinical classes 0 and 1.

At the postoperative evaluation, compared to the non-marked group, patients in the marked group had fewer remaining preoperatively identified reflux sites. As doppler-derived information is used for decision-making and surgery-planning, it seems apparent that preoperative venous marking is beneficial. To my own knowledge, no data exist as to who should perform the preoperative examination and as to ways to communicate this information. In this study, communicating by written information with surgeons did not succeed as well as it could have, since a number of known reflux sites had been left intact. A duplex-based diagram might be more useful and readable for the operating surgeon. Nevertheless, it is essential that the surgeon understands the hemodynamic problem as well as possible. This is probably best achieved by the surgeons’ performing the examination themselves, which is the practice of today. Both Studies I and II underline this approach.

Outcome of ultrasound-guided foam sclerotherapy

Ultrasound-guided foam sclerotherapy seemed effective in eliminating superficial venous reflux and related symptoms. The proportion of patients managing complete success was over 80%. Most patients were satisfied with the treatment, and only a few had complaints.

The occlusion rate after a single session was 90% and decreased in follow-up to 62%. The immediate occlusion rate is in accordance with the rates from other studies (Cabrera et al. 2000, Darke et al. 2006, O'Hare et al. 2008, Wright et al. 2006), but the occlusion rates after a 6 month or longer follow-up have been somewhat higher in other studies (Barrett et al. 2004a, Barrett et al. 2004b, Cabrera et al. 2000, Coleridge-Smith 2006, O'Hare et al. 2008, Wright et al. 2006, Yamaki et al. 2004). No difference existed in treatment results between primary or recurrent GSVs or main branches of the GSV.
DISCUSSION

Coleridge-Smith (2006) has also demonstrated that treatment of recurrent varices can be successful. Elimination of reflux succeeded in 74%. In these cases, the veins were fibrosed or patent but competent with antegrade flow and reduced diameter. According to the efficacy criteria of UGFS, this is a satisfactory outcome (Breu et al. 2008). Whether this recanalization could lead to incompetence and recurrence of varicose veins in long-term follow-up is unclear. It is noteworthy that recanalization does not always translate to clinical recurrence (Barrett et al. 2004a). Interestingly, patency and incompetency of the SFJ was common here. Even after a successful GSV treatment, almost 90% of the junctions remained open or refluxing. Theoretically, this could lead to recurrence.

The most recent systematic review confirmed that UGFS is a safe treatment (Jia et al. 2007). However, a small risk for serious adverse events exists. In fact, we had one case of DVT and PE occurring in our rather small series.

Rates of hyperpigmentation and thrombophlebitis were much higher in our patients (66% and 17%) than the reported median rates, 17.8% and 4.7% (Jia et al. 2007). This might be due to the fact that we defined even the mildest discoloration of the skin as hyperpigmentation, and that the definition of thrombophlebitis was unclear.

This study confirmed the current opinion that UGFS is an effective method for eliminating superficial venous reflux, but long-term follow-up results remain unclear. Since the risk exists for thromboembolic complications, detection of patients at risk, to allow prophylactic or alternative treatment is important.

Comparison of reflux pattern after catheter-directed and systemic thrombolysis

Clinical outcomes 2 to 3 years after catheter-directed or systemic thrombolysis for iliofemoral DVT did not significantly differ. However, the CDT group appeared to have fewer symptoms. The rate of PTS is not clearly reported in the original paper. The C classes at the postoperative evaluation show that 6 patients in the CDT group and 11 in the systemic thrombolysis group experienced venous edema or skin changes, both of which are symptoms of PTS. Thus, the rates would be 38% and 69%. In a recent review comparing the results of CDT and systemic thrombolysis, the rates of PTS were 27% and 57% (Alesh et al. 2007). The length of follow-up was unclear. Park et al. (2008) retrospectively evaluating long-term results of CDT and the feasibility of stent placement in 34 patients with first-time iliofemoral DVT, showed that primary technical success does not necessarily prevent post-thrombotic damage, because the rate of recurrent DVT is high. During the follow-up of mean 47 months, the rate of re-thrombosis was 32% and the rate of PTS 21%. More than half the patients in our study had risk factors such as hypercoagulability and previous DVT which predispose to DVT recurrence. Another factor affecting risk for PTS is the use of compression. Compression stockings are a standard treatment of DVT and reduce the rate of PTS (Brandjes et al. 1997). Our study revealed a compliance problem, as only about half the patients were using compression.

Bleeding complications did not differ between groups, although the small sample size limits this comparison. Rates for major bleeds have ranged between studies from 0 to 38%
for systemic thrombolysis and from 0 to 25% for CDT, depending on diagnostic and follow-up protocols as well as on dosing regimen, duration of infusion, extent of concomitant anticoagulation, and specific thrombolytic agent (Janssen et al. 2005).

Although clinical outcomes were similar in both groups, reflux status differed. Patients treated with CDT had less venous reflux in both deep and superficial veins, but incidence of obstruction was surprisingly high in both groups (31% and 50%). Whether those obstructions represented post-thrombotic occlusion from the initial DVT or from an earlier episode is unclear. A few reports have assessed long-term benefits of thrombolytic therapy in terms of preserved valvular function, and to our knowledge, none have compared systemic and catheter-directed thrombolysis. Three groups have reported the rate of valvular competence or of venous reflux at 6 months after CDT (Elsharawy et al. 2002, Mewissen et al. 1999, Enden et al. 2009). The rate of valvular competence was 38 to 72% depending on the completeness of the lysis (Mewissen et al. 1999), and the rate of venous reflux was 11% (Elsharawy et al. 2002) and 60% (Enden et al. 2009).

The results of this study suggest that catheter-directed thrombolysis may be superior to systemic thrombolysis in preserving venous valvular function. This finding needs to be confirmed in a large prospective randomized trial.

Outcome of deep venous reconstruction

Overall, the results were unsatisfactory. Few of our patients benefited from deep venous reconstruction in the long-term, and most of these suffered primary deep venous incompetence. The clinical success rate and the durability of the different reconstructions was low, mostly due to very poor outcome of operations for post-thrombotic syndrome.

Although the VCSS improved in most patients, any change in mean values was small. Disability score is not a sensitive parameter to measure change in response to treatment in patients who use permanent compression therapy, e.g., those with chronic post-thrombotic changes. In the 2003 validation study of VDS by Kakkos et al., all patients had primary varicose veins.

Satisfactory outcome and the criteria for clinical success are difficult to define in patients with severe CVI. In our study, venous clinical severity scores needed to be 0 to 1 in all fields to represent clinical success, provided that the patient could work or carry out usual activities for 8 hours. Of the patients with congenital or primary CVI, 44% fulfilled these criteria at 4 years, but of the patients with PTS, only 17%. Differences in the definition of success between studies make it difficult to compare the results. Kistner’s group has followed their patients the longest and reported markedly better results: a 10-year cumulative clinical success rate of 73% for primary CVI and of 43% for PTS (Masuda et al. 1994b). In our material, all but one patient with healed or active ulcer at the time of reconstruction had secondary DVI and most often underwent valve transplantation or transposition. The overall cumulative freedom from ulcer at 4 years was 54%, comparable to other published results. The ulcer-free interval at 6 years after valve transplantation in clinical series has been 50 to 65% (Bry et al. 1995, Perrin 2000, Raju et al. 1999).
DISCUSSION

The overall reflux status of patients at the final follow-up visit reflects disease severity. All but three of our patients had some reflux, and more than half had severe incompetence at the site of the reconstruction. Patients with primary or congenital disease fared better: More than two-thirds had a reconstruction that was competent. Other studies have also demonstrated that patients with primary DVI treated with valvuloplasty are most likely to benefit from deep venous reconstruction (Masuda et al. 1994b, Raju et al. 1996, Tripathi et al. 2004). The low cumulative durability rate of internal valvuloplasty in our study is due to the fact that most patients treated with this technique had post-thrombotic syndrome. All but one internal valvuloplasty for primary DVI remained competent.

The most durable technique was external valvuloplasty, with a cumulative durability rate of 71%. However, the small number of these reconstructions (seven) limits comparisons with other trials. In addition, several different techniques for external valvuloplasty exist, and these techniques are not entirely comparable. It seems that the results with Kistner's technique, which we used, are inferior to those of the modifications (Belcaro et al. 1999, Raju et al. 2000a, Sakuda et al. 2002, Wang et al. 2006).

Our results for valve transplantations were poor, with a cumulative durability rate of only 16%. All but one axillary transfer failed. Other clinical studies have reported better but variable results (Perrin 2000, Rosales et al. 2008, Sheridan et al. 2005, Tripathi et al. 2004). Although we used commonly accepted techniques, our limited experience and small number of treated patients probably explain part of the difference in the outcomes. The cumulative durability rate of transpositions was somewhat lower than the reported average rate of competency (Sheridan et al. 2005).

These results show that achieving good outcomes for deep venous surgery as part of routine vascular surgery is difficult. The poor long-term outcome of reconstructions for secondary DVI emphasizes the importance of early active intervention at the time of DVT.
DISCUSSION

Conclusions

In the present studies, some venous reflux was present postoperatively irrespective of the method of evaluation or ablation of the reflux. The results can be summarized as follows:

1. The vascular surgical service succeeded better in the elimination of axial superficial venous reflux than did the general surgical service: Preoperative evaluation with duplex seems to affect the outcome of superficial venous surgery positively.

2. Doppler-derived information could not be communicated preoperatively in written form to surgeons, and surgery was inadequate without preoperative venous marking: Surgeons should perform preoperative venous marking themselves.

3. Ultrasound-guided foam sclerotherapy is an effective treatment of superficial venous incompetence in the early stages of the learning curve in a practice specialized in venous diseases.

4. Active local thrombolysis of iliofemoral deep venous thrombosis reduces later reflux and most probably the development of post-thrombotic syndrome as well.

5. Repair of deep venous insufficiency is demanding. As the results of reconstructions for post-thrombotic syndrome are poor, the focus should be on prevention and active treatment of deep venous thrombosis.
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Helsinki, February 2009
Annamari Oinonen
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Appendices

Appendix I: Quality of life questionnaire 15D (Reprinted with permission of copyright holder Harri Sintonen)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

Question 1. Mobility
1( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4( ) I am able to walk indoors only with help from others.
5( ) I am completely bed-ridden and unable to move about.

Question 2. Vision
1( ) I see normally, ie I can read newspapers and TV text without difficulty (with or without glasses).
2( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4( ) I cannot read papers and/or TV text either with glasses or without, but I can see enough to walk about without guidance.
5( ) I cannot see enough to walk about without a guide, ie I am almost or completely blind.

Question 3. Hearing
1( ) I can hear normally, ie normal speech (with or without a hearing aid).
2( ) I hear normal speech with a little difficulty.
3( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4( ) I hear even loud voices poorly; I am almost deaf.
5( ) I am completely deaf.

Question 4. Breathing
1( ) I am able to breathe normally, ie with no shortness of breath or other breathing difficulty.
2( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4( ) I get shortness of breath even after light activity, eg washing or dressing my self.
5( ) I have breathing difficulties almost all the time, even when resting.

Question 5. Sleeping
1( ) I am able to sleep normally, ie I have no problems with sleeping.
2( ) I have slight problems with sleeping, eg difficulty in falling asleep or sometimes waking at night.
3( ) I have moderate problems with sleeping, eg disturbed sleep, or feeling I have not slept enough.
4( ) I have great problems with sleeping, eg having to use sleeping pills often or routinely, or usually waking at night and/or waking too early in the morning.
5( ) I suffer severe sleeplessness, eg sleeping is almost impossible even with full use of sleeping pills, or staying awake most of the night.

Question 6. Eating
1( ) I am able to eat normally, ie with no help from others.
2( ) I am able to eat by myself with minor difficulty (eg slowly, clumsily, shakily, or with special appliances).
3( ) I need some help from another person in eating.
4( ) I am unable to eat by myself at all, so I must be fed by another person.
5( ) I am unable to eat at all, so I am fed either by tube or intravenously.

Question 7. Speech
1( ) I am able to speak normally, ie clearly, audibly and fluently.
2( ) I have slight speech difficulties, eg occasional fumbling for words, mumbling, or changes of pitch.
3( ) I can make myself understood, but my speech is eg disjointed, faltering, stuttering or stammering.
4( ) Most people have great difficulty understanding my speech.
5( ) I can only make myself understood by gestures.

Question 8. Elimination
1( ) My bladder and bowel work normally and without problems.
2( ) I have slight problems with my bladder and/or bowel function, eg difficulties with urination, or loose or hard bowels.
3( ) I have marked problems with my bladder and/or bowel function, eg occasional ‘accidents’, or severe constipation or diarrhea.
4( ) I have serious problems with my bladder and/or bowel function, eg routine ‘accidents’, or need of catheterization or enemas.
5( ) I have no control over my bladder and/or bowel function.

**Question 9. Usual activities**
1( ) I am able to perform my usual activities (eg employment, studying, housework, free-time activities) without difficulty.
2( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3( ) I am able to perform my usual activities much less effectively with considerable difficulty, or not completely.
4( ) I can only manage a small proportion of my previously usual activities.
5( ) I am unable to manage any of my previously usual activities.

**Question 10. Mental function**
1( ) I am able to think clearly and logically, and my memory functions well.
2( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4( ) I have great difficulties in thinking clearly and logically, or my memory sometimes is seriously impaired.
5( ) I am permanently confused and disoriented in place and time.

**Question 11. Discomfort and symptoms**
1( ) I have no physical discomfort or symptoms, eg pain, ache, nausea, itching etc.
2( ) I have mild physical discomfort or symptoms, eg pain, ache, nausea, itching etc.
3( ) I have marked physical discomfort or symptoms, eg pain, ache, nausea, itching etc.
4( ) I have severe physical discomfort or symptoms, eg pain, ache, nausea, itching etc.
5( ) I have unbearable physical discomfort or symptoms, eg pain, ache, nausea, itching etc.

**Question 12. Depression**
1( ) I do not feel at all sad, melancholic or depressed.
2( ) I feel slightly sad, melancholic or depressed.
3( ) I feel moderately sad, melancholic or depressed.
4( ) I feel very sad, melancholic or depressed.
5( ) I feel extremely sad, melancholic or depressed.

**Question 13. Distress**
1( ) I do not feel at all anxious, stressed or nervous.
2( ) I feel slightly anxious, stressed or nervous.
3( ) I feel moderately anxious, stressed or nervous.
4( ) I feel very anxious, stressed or nervous.
5( ) I feel extremely anxious, stressed or nervous.

**Question 14. Vitality**
1( ) I feel healthy and energetic.
2( ) I feel slightly weary, tired, or feeble.
3( ) I feel moderately weary, tired, or feeble.
4( ) I feel very weary, tired, or feeble, almost exhausted.
5( ) I feel extremely weary, tired, or feeble, totally exhausted.

**Question 15. Sexual activity**
1( ) My state of health has no adverse effect on my sexual activity.
2( ) My state of health has a slight effect on my sexual activity.
3( ) My state of health has a considerable effect on my sexual activity.
4( ) My state of health makes sexual activity almost impossible.
5( ) My state of health makes sexual activity impossible.
Appendix II: Clinical varicose veins questionnaire (Reproduced from Qual Health Care, Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH, 2, 5-10, 1993 with permission from BMJ Publishing Group Ltd.)

1. Please draw in your varicose veins in the diagram(s) below:

   Legs viewed from front   Legs viewed from back

2. In the past two weeks, for many days did your varicose veins cause you pain or ache?
   (Please tick one box for each leg)

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<thead>
<tr>
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<th>Right</th>
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<tbody>
<tr>
<td>None at all</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Between 1 and 5 days</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Between 6 and 10 days</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>For more than 10 days</td>
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3. In the past two weeks at what time of day were your varicose veins usually most painful or aching?
   (Please tick one box)

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<tbody>
<tr>
<td>Not painful at all</td>
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<tr>
<td>No particular time</td>
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<tr>
<td>In the morning</td>
<td>☐</td>
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<tr>
<td>In the afternoon and/or evening</td>
<td>☐</td>
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<tr>
<td>At night</td>
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4. During the past two weeks, on how many days did you take painkilling tablets for your varicose veins?
   (Please tick one box)

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<td>None at all</td>
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<td>Between 1 and 5 days</td>
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<td>Between 6 and 10 days</td>
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<tr>
<td>For more than 10 days</td>
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5. In the past two weeks, how much ankle swelling have you had?
   (Please tick one box)

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<tbody>
<tr>
<td>None at all</td>
<td>☐</td>
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<tr>
<td>Slight ankle swelling</td>
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<tr>
<td>Moderate ankle swelling (for example causing you to sit with your feet up whenever possible)</td>
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<tr>
<td>Severe ankle swelling (for example causing you difficulty putting on your shoes)</td>
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6. In the past two weeks, have you worn support stockings?
   (Please tick one box for each leg)

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<tr>
<td>No</td>
<td>☐</td>
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<tr>
<td>Yes, those I bought myself without a doctor’s prescription</td>
<td>☐</td>
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<tr>
<td>Yes, those my doctor prescribed for me, which I wear occasionally</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Yes, those my doctor prescribed for me, which I wear every day</td>
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</tbody>
</table>

7. Do you take “water tablets” for ankle swelling?
   (Please tick one box)

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<td>No</td>
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<tr>
<td>Yes</td>
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APPENDICES

8. In the past two weeks, have you had any itching in association with your varicose veins?
   (Please tick one box for each leg)

   Right  No [ ]  Yes [ ]
   Left   No [ ]  Yes [ ]

   Yes, but only above the knee [ ]
   Yes, but only below the knee [ ]
   Yes, both above and below the knee [ ]

9. Do you have purple discoloration caused by areas of tiny blood vessel in the skin, in
   association with your varicose veins?
   (Please tick one box for each leg)

   Right  No [ ]  Yes [ ]
   Left   No [ ]  Yes [ ]

   Yes, but does not require any treatment from a doctor or district nurse [ ]
   Yes, and requires treatment from a doctor or district nurse [ ]

10. Do you have rash or eczema in the area of your ankle?
    (Please tick one box for each leg)

    No [ ]  Yes [ ]

11. Do you have a skin ulcer associated with your varicose veins?
    (Please tick one box for each leg)

    No [ ]  Yes [ ]

12. Does the appearance of your varicose veins cause you concern?
    (Please tick one box)

    No [ ]  Yes, slight concern [ ]
    Yes, moderate concern [ ]
    Yes, a great deal of concern [ ]

13. Does the appearance of your varicose veins influence your choice of clothing, including
    tights?
    (Please tick one box)

    No [ ]  Occasionally [ ]
    Often [ ]  Always [ ]

14. During the past two weeks have your varicose veins interfered with your work or
    housework or other daily activities?
    (Please tick one box)

    No [ ]  I have been able to work but my work has suffered to a slight extent [ ]
    I have been able to work but my work has suffered to a moderate extent [ ]
    My veins have prevented me from working one day or more [ ]

15. During the past two weeks have your varicose veins interfered with your leisure activities
    including sport, hobbies, and social life?
    (Please tick one box)

    No [ ]  Yes, my enjoyment has suffered to a slight extent [ ]
    Yes, my enjoyment has suffered to a moderate extent [ ]
    Yes, my veins have prevented me from taking part in any leisure activities [ ]