# Recapping Influential Superficial Venous Trials

A summary of formative published literature with a significant impact to the advancement of superficial venous care.

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Modern venous practice is a complex and dynamic environment involving many professionals and multiple treatment options. It is important to appreciate that high-quality, prospective clinical trials underpin modern clinical practice, including what we do daily. Clinical evidence provides the foundation from which we can be the patient's advocate and offer reliable clinical advice and guidance. Clinical studies are also essential to guide the writing of guidelines and policies, which ultimately persuade payers to fund treatments and change care pathways for patients. Trials are also essential to define gold-standard treatments and reduce unacceptable variations in care that continue to be a challenge in the venous field.

This article aims to highlight and summarize some seminal clinical trials in the superficial venous space. The list is nonexhaustive, and given the space limitations, there are numerous high-quality studies not mentioned. It is difficult to define "impact" when it comes to clinical trials. Traditional bibliometrics such as journal impact factor or number of citations are helpful but often do not describe the full importance of a study. The highest-impact trials have changed the paradigm for clinical treatment for a particular condition or patient group. This impact affects not only the immediate future, but generations to come. It is difficult to overstate how challenging it can be to design, fund, perform, analyze, and disseminate the findings from a clinical trial, particularly a multicenter randomized study. Clinical research and clinical practice are two sides of the same coin with strong interdependence, and I would strongly advocate research activity for all clinicians to reinforce this link.

## VENOUS EPIDEMIOLOGY STUDIES

When managing any chronic condition, particularly venous disease, any discussion with the patient starts with explanation of the diagnosis and natural history of the disease. Without understanding these fundamentals, it is difficult to contextualize the potential benefit of any intervention. It is for this reason I have included important venous epidemiologic studies in this article. These large, longitudinal studies are notoriously challenging to perform, and although our understanding of the progression of venous conditions is far from complete, historic epidemiologic studies have provided important insights.

### Edinburgh Vein Study

In this study, which started in 1995, 1,566 randomly selected adults (aged 18-64 years) from Edinburgh, Scotland, were included and underwent a range of clinical, questionnaire, and duplex ultrasound assessments over an extended follow-up period. The extensive findings have been published in multiple papers over several decades,[1,2] but some important insights are summarized below. Specifically, the Edinburgh Vein Study:

- Provided an estimate for the prevalence of venous disease in the general population, which at up to 40% in some groups, was higher than previously appreciated
- Demonstrated a link between venous reflux and specific symptoms in the legs
- Showed an association between higher body mass index and both prevalence and severity of venous disease and linked patient height to venous reflux (more reflux in taller patients)
- Described the patterns of venous reflux in a large cohort with venous disease
- Showed that for each year of follow-up, 1% of this adult population developed new venous reflux
- After 13 years, around one-third of adults with varicose veins developed skin changes

Most of the novel findings from this study have been substantiated by other international research, and many of these principles are now considered "core" knowledge for all venous practitioners.

### Bonn Vein Study

Between 2000 and 2002, the Bonn Vein study assessed > 3,000 German adults with quality-of-life (QOL) questionnaires and clinical assessments.[3] The symptoms and prevalence of venous disease were similar to the Edinburgh Vein Study. A follow-up study at around 6 years provided an interesting insight into disease progression. An increase in CEAP (clinical, etiologic, anatomic, and pathophysiologic) classification was seen in up to 31.8% of participants, with age and obesity shown to be risk factors for progression.

## EARLY TRIALS EVALUATING OPEN SURGERY

Saphenous high ligation (with the later addition of vein stripping) was the traditional treatment for superficial venous reflux for over a century. Ligation of the saphenous vein was described by Friedrich Trendelenburg in 1890, with vein stripping then advocated by William W. Babcock and others in the early 20th century.

### REACTIV Trial

The REACTIV trial included > 1,000 participants sorted into multiple randomized or observational studies, with the specific aim of evaluating the cost-effectiveness of intervention for superficial venous reflux.[4] One study randomized 246 participants to either conservative treatment or varicose vein open surgery. This is one of the very few high-quality clinical trials with conservative management as one of the study groups. Using robust health economic evaluation, this was one of the first trials to demonstrate that surgery for varicose veins was highly cost-effective compared to conservative management. This study showed that it is worthwhile treating patients with superficial venous disease and subsequent treatment developments have only been possible with this robust foundation.

### Surgical Stripping Versus Ligation Alone

In a study by Dwerryhouse and colleagues, 100 patients (133 legs) with great saphenous vein (GSV) reflux were randomized to junction ligation alone or ligation plus GSV stripping.[5] The results were stark and showed that reoperation rates were three times higher for patients treated with ligation alone. Stripping of the GSV became the standard for open surgical intervention, which in turn has inspired the endovenous ablation modalities that aim to mimic surgical stripping by ablating the GSV. Interestingly, the 11-year follow-up study showed a varicose vein recurrence rate of > 60%.[6]

## TRIALS COMPARING ENDOVENOUS INTERVENTIONS TO SURGICAL STRIPPING

Although sclerotherapy procedures have been used for decades, use of catheter-based endovenous ablation modalities has increased since the early 2000s, and endovenous thermal ablation (ETA) is widely considered the gold-standard treatment for superficial venous reflux. With many new treatment options entering the market, dozens of clinical trials have been performed comparing different endovenous modalities or an endovenous modality with surgical stripping. Several meta-analyses and guideline documents have been published.

### Rasmussen et al Study

In a study that has not been repeated, Rasmussen and colleagues randomized 500 participants (580 legs) with GSV reflux to one of four treatment modalities (laser ablation, radiofrequency ablation [RFA], foam sclerotherapy, or surgical stripping).[7] The study demonstrated higher recanalization and reintervention rates after foam sclerotherapy compared to other modalities. Recovery was quickest after RFA and foam sclerotherapy (compared to laser ablation or surgical stripping). Interestingly, despite these observed differences, the improvements in QOL and clinical disease severity were similar across all four groups.

### CLASS Trial

The CLASS trial was a United Kingdom–based, complex multicenter, randomized controlled trial comparing surgical stripping, foam sclerotherapy, and endovenous laser ablation.[8] A total of 798 participants were included. Although not all centers randomized to all three treatments, a three-way analysis was performed, and the primary outcome measure was QOL at 6 months. Although improvements in QOL were seen in all groups, the health gain achieved was lowest in the group randomized to foam sclerotherapy.

Health economic analysis clearly favored endovenous laser ablation as the strategy most likely to be cost-effective.[9] This, along with multiple other studies and meta-analyses, has resulted in ETA being considered as the gold standard and first-line intervention for the treatment of superficial venous reflux. Most guidelines do not distinguish between different ETA modalities, which is most likely a pragmatic approach given the sheer number of thermal ablation options available.

## VENOUS LEG ULCER TRIALS

Venous leg ulcers (VLUs) represent the most extreme end of the spectrum of venous disease. Since duplex ultrasound became more widely utilized (from the 1990s), several studies reported the very high prevalence of superficial venous reflux in patients with active or healed VLUs, which is contrary to the dogma that ulcers are usually due to deep venous disease. The role of superficial venous intervention in patients with VLUs has been defined by two seminal trials.

### ESCHAR Trial

Between 1999 and 2002, 500 patients with active (C6) or healed (C5) VLUs were randomized to compression alone (the standard of care at the time) or compression with superficial venous surgery.[10] As the ESCHAR trial was conducted before the availability of endovenous interventions, superficial venous surgery consisted of surgical stripping or junction ligation alone under local anesthesia. At 4 years, a significantly lower ulcer recurrence rate was seen in participants randomized to compression plus surgery (31% vs 56%).[11] The advantage was also seen in patients with deep reflux, debunking the myth that superficial venous reflux should not be treated in the presence of deep venous reflux. The main limitations of the trial related to the intervention. Surgical stripping was often very unattractive to the elderly and often frail patient population with VLUs.

### EVRA Study

As endovenous interventions became more widespread, a clinical trial was urgently needed to evaluate the role of these minimally invasive interventions in the population with leg ulceration. The EVRA study included 450 participants with open VLUs and superficial venous reflux from 20 United Kingdom sites.[12] Randomization was to standard care (compression therapy with deferred endovenous ablation of reflux) or early intervention (compression with early endovenous ablation, < 2 weeks). Endovenous intervention was left to the discretion of the treating center. Interestingly, foam sclerotherapy was used in most patients and was the only modality used in > 50%. In every domain assessed, the study demonstrated a clear advantage in favor of early intervention. Specifically, early endovenous intervention resulted in:

- Accelerated VLU healing
- Fewer VLU recurrences
- A highly cost-effective treatment strategy (even cost-saving in many cases)[13]

The EVRA study findings have provided a strong impetus for changing clinical guidelines and VLU treatment pathways worldwide. Positive changes have already occurred but more needs to be done to create referral pathways between primary care and wound care settings (where many of these patients are initially assessed and treated) and venous specialists who can provide the expertise to deliver prompt endovenous treatments.

## CONCLUSION

Unlike many aspects of clinical practice, the use of superficial venous interventions has a strong and robust evidence base. We understand that venous disease is common, and the natural history for untreated venous disease is gradual, but inexorable progression of disease. Intervention is superior to conservative management. Surgical stripping, foam sclerotherapy, and ETA are all effective, but thermal ablation is likely to be superior to foam sclerotherapy (inferior vein closure) and surgical stripping (slower recovery). For patients with VLUs, early endovenous ablation of superficial reflux leads to quicker healing, fewer ulcer recurrences, and strong health economic benefits.

It is important that we continue to support new clinical trials to help define the potential roles of nonthermal endovenous modalities (eg, cyanoacrylate glue closure) or novel treatment strategies (eg, prophylactic ablation of competent accessory saphenous veins). As a community of venous enthusiasts, it is important that we continue to advocate for positive changes to patient treatment pathways and to reflect the available evidence. Only then will we be able to translate the enormous research efforts highlighted in this article into true clinical benefit for our patients. ■

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