Systematic Review of Clinical Effectiveness and Cost-effectiveness of Radiofrequency Ablation for the Treatment of Varicose Veins

A West Midlands Health and Technology Assessment Collaboration Report

Authors: Yaser Adi[1], Lead Systematic Reviewer
Sue Bayliss[1], Information Specialist
Rod Taylor[1], Senior Reviewer

[1]West Midlands Health Technology Assessment Collaboration,
Department of Public Health & Epidemiology,
University of Birmingham

Correspondence to: Dr Y. Adi
Systematic Reviewer
West Midlands Health Technology Assessment Collaboration
Department of Public Health and Epidemiology
University of Birmingham
Edgbaston
Birmingham B15 2TT
United Kingdom

Tel: 0121 414 7865
Fax: 0121414 7878
E-mail: y.adi@bham.ac.uk

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West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost utility analysis) of the intervention.

About InterTASC

WMHTAC is a member of InterTASC, which is a national collaboration with three other units who do rapid reviews: The Trent Working Group on Acute Purchasing; The Wessex Institute for Health Research and Development; The York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing quality control of reports.

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Contribution of authors

Y. Adi was the lead reviewer. He wrote the protocol, liaised with experts, searched and extracted data from the literature, which was checked by two other reviewers, critically appraised the effectiveness data, and helped in conducting the economic analysis. He wrote the initial draft. S. Bayliss performed electronic database and internet searches and read and commented on the final draft. RS Taylor provided advice and support at all stages of this work. He helped in writing the economic analysis. He read and commented on the final draft.

Conflict of interest

This work has been undertaken by people funded by the NHS. The authors have received no funding from any sponsor in this work.

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the use of Radiofrequency Ablation for the Treatment of Varicose Veins:

Borderline

Anticipated expiry date: January 2008

- This report was completed in October 2004
- The searches were completed in January 2004

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Summary

Objective: To systematically review the clinical effectiveness and the cost/cost-effectiveness of studies of radiofrequency ablation (RFA) for the treatment of varicose veins.

Data sources: A number of bibliographic databases were searched. MEDLINE, EMBASE, Cochrane Library; specialist economic databases (i.e. NHS Centre for Reviews and Dissemination Economic Evaluation Database - NHS EED and Office of Health Economics, Economic Evaluations Database – HEED); registers of ongoing research (i.e. National Research Register, metaRegister of Controlled Trials, MRC Clinical Trials Register, and ClinicalTrials.gov); and websites of HTA agencies

Inclusion criteria:

Population: patients with complicated varicose veins. Complications include venous incompetence (confirmed by Doppler or Duplex screening), oedema, venous ulceration, varicosity bleeding, changes in local skin colour, skin eczema and lipodermatosclerosis. Patients with uncomplicated varicose veins will be excluded.

Intervention: Radiofrequency ablation (RFA) used as a single therapy, or in combination with other therapies.

Comparator: conventional surgical therapies for varicose veins including stripping and/or ligation, other surgical approaches or no comparator. Non-surgical interventions (e.g. drug, sclerotherapy, bandaging) were excluded.

Outcomes: *Primary outcomes*: improvement of symptoms of which pain is one, quality of life or severe adverse events (i.e. mortality, deep vein thrombosis, pulmonary embolism). *Secondary outcomes*: varicose vein recurrence, varicose vein re-operation, reflux recurrence, patient satisfaction, health care resource utilisation (e.g. time in hospital)

Data extraction, quality assessment and synthesis: Inclusion/exclusion of the potential studies carried out by two reviewers independently. Data and quality was extracted by one reviewer and checked by another. Numerical pooling was not possible given clinical heterogeneity.

Quantity of data: Two RCTs and seventeen case series met the inclusion criteria.

Results: 2 RCTs of short follow up (8 weeks in one and 4 months in the second) with total patients n=113, Jadad's score (2, 1) showed statistically significant improvements in pain in the post-operative period compared with stripping in one RCT and compared with S&L in the second RCT. QoL was also statistically significant in favor of RFA in the first week following the surgery. Days to return to work were statistically fewer in RFA.
No difference was reported for recurrence of varicose veins. No statistically significant difference in the rate of adverse events except for the ecchymosis and haematoma which was less in RFA. The case series were generally poor due to large

loss to follow up, potential selection bias and lack of masking the assessor. The incremental cost per QALY of RFA compared to stripping was estimated: £23,750 95% CI (£14,074 to £63,333).

Conclusion: RFA is not available on NHS in the UK and those studies of patients who have had RFA may be a selected group of patients usually of higher economic status who are looking for a quick yet cosmetically pleasing answer to their problem. It may also explain why some of the patients are more willing to get back to work as soon as possible. The evidence from the two identified RCTs of poor quality suggests short-term benefit in terms of improvements in pain and quality of life and shorter sick leave relative to conventional surgery. The long-term outcomes of RFA have not yet been well established by comparative studies. One cost study shows that although RFA is more expensive it appears to be cost saving for society.

Abbreviations

CEAP	Clinical signs, Etiologic problems, Anatomic distribution of the process, Pathophysiolgical nature of the dysfunction
CI	Confidence interval
DVT	Deep vein thrombosis
GSV	Greater saphenous vein
ITT	Intention to treat
PE	Pulmonary embolism
QALY	Quality Adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RFA	Radio frequency ablation
SD	Standard deviation
S & L	Stripping and ligation
VAS	Visual Analogue Scale

1. Aim and objectives of the review

The *aim* is to assess the clinical and the cost effectiveness of studies of radiofrequency ablation technique (RFA) for the treatment of varicose veins.

The *objectives* were to systematically review the clinical effectiveness and the cost/cost-effectiveness of studies of radiofrequency ablation.

The *question* to be answered in this review is: in patients with varicose veins does RFA compared with conventional surgical methods improve outcomes or cost effectiveness?

2. Background

Recent press reports have generated considerable interest in a new technique, the RFA which has been introduced as a minimally invasive treatment alternative for patients with varicose veins, claiming major advantages over conventional surgery. The main aim stated was to reduce operative trauma and consequent bruising associated with stripping surgery, leading to quicker postoperative recovery and less scars and therefore more patient satisfaction with the outcomes.

The RFA method has been promoted to close off the long saphenous vein under ultrasound control avoiding a groin incision and gaining access to the vein by a small incision or puncture near the knee.

Many vascular surgeons have regarded the claims of the advertised success of the new treatments for varicose veins with some scepticism because of the lack of robust evidence, the longer operating time and the greater expense.[1] The new treatments are radiofrequency ablation, the long saphenous vein can also be obliterated using a laser probe, the novel application of sclerotherapy and the illuminated powered phlebectomies which involves a suction device with guarded blades which removes veins like a vacuum cleaner.

2.1. Description of underlying health problem

2.1.1.Definitions and Classifications

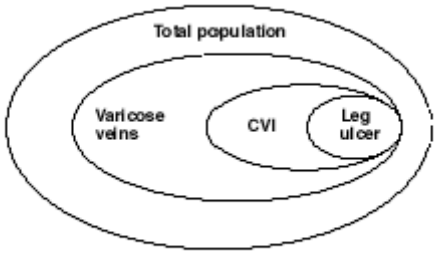
A standard definition of what constitutes a varicose vein has not yet been agreed. The Oxford Medical Dictionary defines them as 'veins that are distended, lengthened and tortuous'[2]. Porter described varicose veins as dilated, palpable subcutaneous veins generally larger than 4mm.[3] The World Health Organisation defines them as 'saccular dilatation of the veins which are often tortuous'. [4] However, these definitions, taken literally, could be restrictive and unhelpful to a commissioner of health care, who will be faced with conditions that the definition would exclude but which are often referred to under the umbrella heading of varicose veins or, more broadly, venous disease.

Any vein may become varicose, but the term varicose vein conventionally applies to varices of the superficial leg veins. In the absence of a precise definition of varicose veins, it is important to understand broadly what varicose veins are and what causes them. The condition is caused by poorly functioning valves within the lumen of the veins. Blood flows from the deep to the superficial venous systems through these incompetent valves, causing persistent superficial venous hypertension, which can lead to varicosity of the superficial veins. However, in the majority of patients have primary superficial valve incompetence causing superficial venous reflux. Common sites of valvular incompetence include the saphenofemoral and saphenopopliteal junctions and perforating veins connecting the deep and superficial venous systems along the length of the leg.[5]

Varicose veins can be classified as trunk, reticular, or telangiectasia. Telangiectasia is also referred to as spider veins, star bursts, thread veins, or matted veins. Most varicose veins are primary. Secondary to conditions include pregnancy, deep vein thrombosis and occlusion, pelvic tumours, or arteriovenous fistulae.

Venous disease is the most common vascular condition to affect the lower limb.[6] The term 'chronic venous disorders of the leg' covers a wide range of conditions, including asymptomatic incompetence of venous valves, venous symptoms, telangiectases, reticular veins, varicose veins, oedema, skin changes and leg ulceration. These can be broadly categorised into varicose veins, chronic venous insufficiency (CVI) and venous ulcers. The relationship between these conditions in the general population is illustrated in (Figure 1)**.**

Figure 1: **The relationship between varicose veins, chronic venous insufficiency and leg ulceration in the population**



Source: Callum 1999

There are a number of classification systems for varicose veins that are widely used, but they are usually incorporated into classifications of venous disease and are based on clinical severity (Table 1). Few classification systems use objective measurements.

Table 1: Classification of varicose veins and chronic venous disease of the leg

Author	Class	Definition
Widmer (1978)[7]		Varicose veins
	1	Hyphenwebs: intradermal venectasis
	2	Reticular varices: dilated tortuous veins, not belonging to the main trunk or its major branches
	3	Trunk varices: dilated, tortuous trunks of the long or short saphenous vein and their branches of the first or second order.
		Each category is graded 1-3 according to the degree and extent of tortuosity and prominence.
		Chronic venous insufficiency
		Categorised into grades I, II and III according to the presence of dilated subcutaneous veins, skin changes and ulceration.
Porter (1988)[8]	0	Asymptomatic
	1	Mild, i.e. mild to moderate ankle swelling, mild discomfort, and local or generalised dilation of subcutaneous veins. Usually superficial veins only.
	2	Moderate, i.e. hyperpigmentation of the skin, moderate brawny oedema, and subcutaneous fibrosis. There is usually prominent local or regional dilatation of the subcutaneous veins.
	3	Severe, i.e. chronic distal leg pain associated with ulcerative or pre-ulcerative skin changes, eczematoid changes, and/or severe oedema. Usually involves the deep venous system with widespread loss of venous valvular function and/or chronic deep vein obstruction.
CEAP (1995)[9]	0	No visible or palpable signs of venous disease
	1	Telangiectases or reticular veins (also called spider veins/thread veins/star bursts/matted veins)
	2	Varicose veins
	3	Oedema
	4	Skin changes ascribed to venous disease (e.g. pigmentation, venous eczema, lipodermatosclerosis)
	5	Skin changes (as defined above) in conjunction with healed ulceration
	6	Skin changes (as defined above) in conjunction with active ulceration

The most recent classification system to be published is the CEAP classification. This is based on clinical signs, etiologic classification, anatomic distribution and pathophysiologic dysfunction (CEAP). It was developed to provide a comprehensive, objective classification that could be promoted worldwide.
The ease of application of the CEAP classification and its validity has yet to be formally assessed.[10]

2.1.2 Epidemiology

Incidence

The Framingham Study[11] followed up men and women who were living in Framingham, USA. Every 2 years from 1966 over a 16-year period, subjects were examined for varicose veins. Over the 16 years, 396 of 1720 men and 629 of 2102 women who were initially free from varicose veins developed varicose veins. The biannual incidence rate of varicose veins was to be 2.6% in women and 2.0% in men. The incidence rate beyond the age of 40 years was constant.

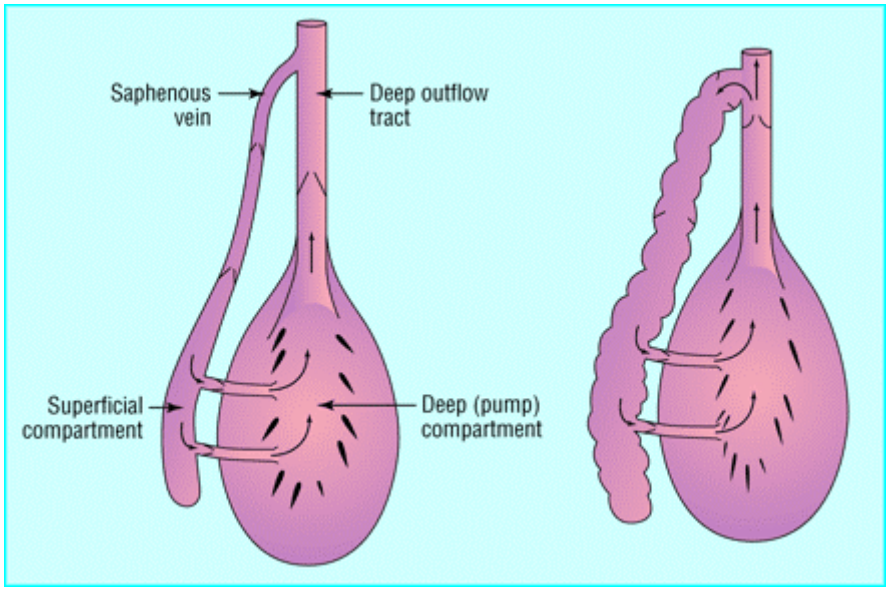
Prevalence

The prevalence of varicose veins in Western populations has been estimated in one study to be about 25–30% among women and 10–20% in men. A recent Scottish cohort study has, however, found a higher prevalence of varices of the saphenous trunks and their main branches in men compared to women (40% men and 32% women).[12]

Aetiology

The theory that varicose veins result from failure of valves in the superficial veins leading to venous reflux and vein dilatation has been superseded by the hypothesis that valve incompetence follows rather than precedes a change in the vein wall. Thus, the vein wall is inherently weak in varicose veins, which leads to dilatation and separation of valve cusps so that they become incompetent. This theory is strongly supported by the observation that the dilatation of varicose veins is initially distal to the valve; if the primary abnormality was descending valve incompetence, the initial dilatation should be proximal to the valve.[13] Figure 2.

Figure 2 The mechanisms of failure of calf muscle pump and venous hypertension.



(Source: London and Nash 2000)

Superficial veins do not normally allow reflux of blood (left). However, if superficial veins are incompetent (right), some of the blood ejected by the calf muscle pump during systole refluxes back down the superficial veins into the calf muscle pump during diastole. This retrograde circuit can overload the calf muscle pump, leading to dilatation and failure. The subsequent rise in end diastolic volume leads to venous hypertension.

2.1.3 Risk factors

Risk factors summarised by Health Care Need Assessment in a recent publication[14] for varicose veins include fixed factors - female sex, age, pregnancy, ethnicity, geographic location, family history - and potentially preventable factors - obesity, occupations requiring prolonged standing or sitting, lack of dietary fibre. The VEINES Task Force found that aside from age and sex, evidence linking most factors to varicose vein development is limited, and concluded that the evidence was adequate only for pregnancy and obesity. The findings on the aetiology of primary varicose veins do not suggest that there is large scope for primary prevention.

Sex

It is generally believed that women are more commonly affected by varicose veins than men and most studies have shown a female predominance of varicose veins but in the majority of studies the sex ratio decreases with increasing age.

However, Edinburgh vein study found that there was a significantly higher prevalence of trunk varices in men compared with women.[16]

Age

The association between age and prevalence of varicose veins is fairly conclusive. The majority of surveys show a steady increase in prevalence of varicose veins with increasing age for all grades of varicosity. The increase, however, was not as significant in the older age groups.

Pregnancy

It is generally believed that pregnancy leads to varicose veins due to the pressure of the uterus obstructing venous return from the legs. However, this has been refuted, as the majority of varices appear during the initial 3 months when the uterus is not large enough.[15] A hormonal factor is thought to be responsible or the increased circulating volume of blood.

Ethnicity and western lifestyle

A striking feature of the epidemiological studies of varicose veins is a marked geographical variation in prevalence rates, suggesting a possible association with ethnic group or with lifestyle factors. Several studies suggest that varicose veins are rare in Africa and other developing countries when compared to Western societies.

Family history

A number of studies have found that the risk of varicose veins was higher in those with affected relatives.

Body weight and height

Several authors have found an association between weight and body mass and an increased risk for varicose veins. A positive correlation with varicose veins was found in many studies but no correlation was found in other studies.

Occupation

A person's occupation has been put forward as a possible risk factor for varicose veins. A standing occupation has been indicated in some studies as a significant risk factor for varicose veins although this has been found to be insignificant in other studies and was even refuted in others.

Other risk factors:

Smoking

A correlation between cigarette smoking and varicose veins was found among men in the Framingham Study but other studies have shown no relationship between cigarette smoking and varicose veins.

Constipation

A diet deficient in fibre has been implicated as a major factor in the causation of varicose veins.

Social class

In the Edinburgh vein study there was no obvious relation between social class (classified by occupation) and the age and sex-adjusted prevalence of trunk varices.

Post- thrombotic limb

Post-thrombotic limb is the term used to describe venous insufficiency when there is evidence of previous deep vein thrombosis (DVT). Studies have reported frequencies between 5% and 10% of patients having an acute DVT.

2.1.4 Symptoms of varicose veins

Prevalence of leg symptoms:

Women were more likely than men to have lower leg symptoms (Table 2), despite fewer women having trunk varices than men (32% versus 40% age-adjusted prevalence).

Table 2 Age-adjusted prevalence (%) of leg symptoms in men and women

Leg symptoms	Men (n=699)	Women (n=867)	P value
Heaviness or tension	16.0	28.6	≤0.010
Feeling of swelling	9.2	23.0	≤0.010
Aching	32.5	53.8	≤0.010
Restless legs	20.0	35.1	≤0.010
Cramps	34.0	42.0	≤0.010
Itching	19.0	25.3	≤0.010
Tingling	16.0	19.8	0.084
Source: Bradbury *et al*[16]			

Complications of untreated varicose veins:

London and Nash reported in their review some complications of varicose veins, such as haemorrhage and thrombophlebitis that result from the varicose veins themselves, whereas others, such as oedema, skin pigmentation, varicose eczema, atrophie blanche, lipodermatosclerosis, and venous ulceration result from venous hypertension. The size of varicose veins does not seem related to the degree of venous hypertension because 40% of limbs with ulceration due to superficial venous incompetence do not have visible varicose veins. The recognised complications of varicose veins are:

- Haemorrhage
- Thrombophlebitis
- Oedema
- Skin pigmentation
- Atrophie blanche
- Varicose eczema
- Lipodermatosclerosis
- Venous ulceration

2.1.5 Natural history of varicose veins

There is a general lack of data concerning the way varicose veins develop, and at what point treatment could be advised as being a prophylactic rather than remedial there have been no prospective long term studies identified which have measured the risk of developing skin changes and laceration from asymptomatic or mild varicose veins.

Varicose vein does not always lead to ulceration and not all ulcers are secondary to deep venous reflux.

Varicosities developed during pregnancy do regress. Little is known about the rate of progression and there is little known about the factors, which modify it. However when varicose veins have developed following DVT, the pathogenesis of the resulting chronic venous insufficiency is different from that which is due to incompetence of the superficial venous system.

The crucial role of incompetent perforating veins in the lower leg and ankle has been accepted although the strength of association is open to question.[17] As it is not clear what risks asymptomatic and mild varicose veins carry with them for precipitating skin changes and ulceration, its not clear whether all such things should be treated.

Once there is clear evidence and the natural history of the varicose veins and their contributions to ulceration, then treatment options will become clearer.

It is generally accepted that once veins have become distended and torturous, there is no way in which they will return to a normal condition. Whether the propensity to develop varicose vein is an inexorable disease that can be relieved but not cured is still not clear- if it is then, it is highly unlikely that it is preventable.[18]

2.1.6 Effectiveness of assessment methods

In assessing data on the reliability and validity of diagnostic tests the Task Force considered studies that had moderate to strong scientific evidence.

Clinical examination

None of the studies retained by the Task Force allowed formal assessment of the validity of the Trendelburg test for diagnosing venous valvular incompetence, although there is some evidence to suggest it may help predict functional improvement after vein stripping surgery.

Doppler

A hand-held Doppler provides clear answers regarding the presence or absence of reflux at the sapheno-femoral and/or sapheno-popliteal junctions in 90% of patients when used by an experienced practitioner.

Duplex scanning

Studies assessing the validity of duplex scanning in detecting the site and severity of reflux compared to descending phlebography and venous pressure measurement found that sensitivity for deep vein reflux was 0.79-1.0, but specificity was only 0.63-0.88.

Phlebography

Descending phlebography has high sensitivity but low specificity for the detection of deep reflux when compared to venous pressure measurement.

2.2. Current service provision

Conservative treatment

The aim is to improve venous return and reduce pressure in varicose superficial veins. It should be considered in:

- patient's with uncomplicated varicosities
- the pregnant, the elderly

Methods include:

Encourage walking, discourage prolonged sitting or standing, keep legs elevated when sitting to increase venous return, lose weight, if appropriate, wear supporting elastic stockings which compress superficial veins.

Sclerotherapy

Injection sclerotherapy is indicated for small disfiguring varicose veins (usually below the knee) without junctional incompetence. It is done as an outpatient procedure. Injection sclerotherapy for varicose veins has been used widely since 1963, and was reviewed in a Cochrane Library in 2003 and in which the reviewers stated the evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins following surgery, and thread veins. A comparison of surgery versus sclerotherapy is needed.[19]

Surgery

The most common form of surgery for varicose veins consists of flush ligation of the sapheno-femoral junction, which is also called high saphenous ligation.

2.3 Volume of Conventional surgery for varicose veins

There were approximately 70,000 operation (ligation or stripping) carried out in England and Wales in 1997-1998.[20] (Table 3)

Table 3 Varicose vein operations (ligation or stripping) in England &Wales 1997-1998

	Independent Hospitals			NHS Hospitals		
Funding	Private	NHS	Total	Private	NHS	Total
Ligation or stripping	12782	733	21186	505	48340	48845

In the West Midlands, there were 17401 elective varicose vein procedures in year 2002/2003 (source HES2).

2.3.1 A guideline for patients referral

The National Institute of Clinical Excellence has published a guide to appropriate referral from general practice to specialist services for varicose veins.[21] The guide emphasises that most varicose veins require no treatment and says that the key role of primary care is to provide reassurance, explanation and education. Table 4 outlines the referral advice for referral to a specialist service in patients in whom varicosities are present or suspected. Table 4

Table 4 Referral advice for patients in whom varicosities are present or suspected

Referral timings	Condition
Patient is seen immediately (within a day)	Patient is bleeding from a varicosity that has eroded the skin
Patient is seen urgently (max. 2 weeks wait recommended)	Patient has bled from a varicosity and is at risk of bleeding again
Patient is seen soon	Patient has an ulcer which is progressive and/or painful despite treatment
Patient has a routine appointment	Patient has an active or healed ulcer and/or progressive skin changes that may benefit from surgery
	Patient has recurrent superficial thrombophlebitis
	Patient has troublesome symptoms attributable to their varicose veins, and/or they and their GP feel that the extent, site and size of the varicosities are having a severe impact on quality of life

Source: National Institute of Clinical Excellence 2001

In September 2003, The National Institute for Clinical Excellence (NICE) issued a guidance based on one RCT and 4 case series[22] (i.e. not a systematic review). This guidance stated that the current evidence on safety and efficacy of RFA of varicose veins appears adequate to support the use of this procedure as an alternative to S&L

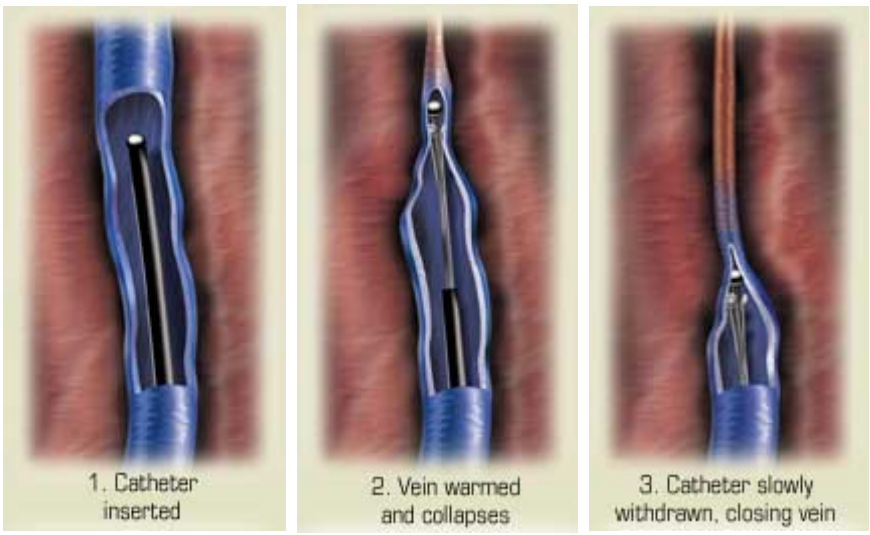
provided that the normal arrangements are in place for consent, audit and clinical governance. NICE also stated that most specialist advisors believe that RFA is a novel procedure. They quote similar risk and benefits and the advisors were concerned about a lack of long-term results regarding the efficacy of the procedure, particularly around the risk of recurrence. The specialist advisors noted that RFA is mostly used in private practice in the UK, and several felt it was unlikely to disseminate widely in the NHS.[23]

2.4. Description of the new intervention

The VNUS Closure procedure has been introduced by VNUS Medical Technologies as a minimally invasive option for many patients with varicose veins. Using radiofrequency (RF) energy and a catheter based approach; the Closure procedure occludes veins thereby eliminating reflux. The device was given clearance from the licensing authorities, CE Mark approval, in 1998 and USA FDA clearance in 1999 as well as Australian approval allowing registry studies in the three countries.

Radiofrequency ablation (RFA) of the saphenous vein results in obliteration of the vein because of the combination effect of collagen contraction of the vein wall and because of the thrombosis in the residual vein lumen, therefore, RFA has been introduced to provide an alternative to traditional vein stripping. Figure 3.

Figure 3 The VNUS Closure procedure



Source VNUS Medical Technologies[24]

The zone of thermal damage is limited to 2 mm beyond the point of contact with the electrodes. The lumen should be completely ablated in most areas, with some portions

of the vessel demonstrating a small residual lumen containing organized fibrous thrombi. Birefringence is present, and new collagen growth is evident.

Present radiofrequency ablation catheters cannot be easily passed along a tortuous superficial vein; therefore, the procedure is principally of use in the treatment of truncal varicose veins, such as the greater saphenous vein, with saphenofemoral incompetence.

Pre-procedure

Ultrasonography is used to confirm and map all areas of reflux and to trace the path of the refluxing greater saphenous trunk from the saphenofemoral junction down the leg to the upper part of the calf. An appropriate entry point is selected just above or just below the knee, at a point permitting cannulation of the vessel with a 16-gauge needle introducer. The vein, the saphenofemoral junction, and the anticipated entry point are marked on the skin with a surgical marker.

The procedure

The leg is prepared and draped, and a local anaesthetic agent is used to anaesthetize the site of cannulation. Needle puncture of the vessel is guided by ultrasonography. The Seldinger technique is used to place a guide wire into the vessel, and an introducer sheath is passed over the guide wire, which is removed. The Closure catheter is passed through the sheath, and the tip is advanced to the saphenofemoral junction under ultrasonographic visualization.

With ultrasonographic guidance, a diluted local anesthetic agent is injected into the tissues surrounding the greater saphenous vein within its fascial sheath. The anaesthetic is injected along the entire course of the vein from the catheter insertion point to the saphenofemoral junction.

Ultrasonography is used to position the catheter tip at the level of the terminal valve of the saphenofemoral junction, and the catheter electrodes are deployed. The electrodes should be just distal to the valve cusps of the terminal or subterminal valve, but the catheter must not extend into the femoral vein because injury to the femoral vein may cause deep vein thrombosis.

When the console is switched on and the test mode is activated, the baseline impedance should be 250-300 ohms and the baseline temperature should be 32-37°C. When radiofrequency energy is applied, the thermocouple temperature should rise to 80-85°C within 10-15 seconds. After the temperature reaches 85°C and remains constant for 15 seconds, the catheter tip is slowly withdrawn at a rate of approximately 1 cm per minute. After the catheter tip is 4 cm below the saphenofemoral junction, the rate of withdrawal is increased to approximately 2.5 cm per minute (1 mm every 2-3 seconds).

Post-procedure

Post-treatment sonograms confirm the contraction of the vessel and the absence of flow along the entire length of the treated vessel. If persistent flow is observed, the procedure may be repeated immediately, provided the catheter can still be easily passed along the vessel to the desired site of treatment.
Compression is of vital importance after any venous procedure. Compression is effective in reducing postoperative bruising and tenderness, and it can also reduce the risk of venous thromboembolism in both the treated leg and the untreated leg.
The patient is re-evaluated 3-7 days after the operation, at which time duplex sonograms should demonstrate a closed greater saphenous vein and no evidence of thrombus in the femoral, popliteal, or deep veins of the calf.

At 6 weeks, an examination should reveal clinical resolution of truncal varices, and an ultrasonographic evaluation should demonstrate a completely closed vessel and no remaining reflux.

3. Methods

3.1 Search strategy

A number of bibliographic databases were searched: MEDLINE, EMBASE, Cochrane Library, specialist economic databases (i.e. NHS Centre for Reviews and Dissemination Economic Evaluation Database - NHS EED and Office of Health Economics, Economic Evaluations Database – HEED); registers of ongoing research (i.e. National Research Register, metaRegister of Controlled Trials, MRC Clinical Trials Register, and ClinicalTrials.gov); and websites of HTA agencies (HSTAT, DIHTA, SINTEF, AETMIS, NZHTA, CCOHTA, INAHTA, York CRD, NICE, NCCHTA, Alberta Heritage Foundation). Searches were conducted in January 2004. Details of search terms used are provided in Appendix 4 and 5.
Hand searching of the reference lists of included studies and reviews was undertaken. The manufacturer of the radio frequency ablation device (VNUS Medical Technology) was contacted to identify any further studies. Two identified authors of the included studies were contacted to provide any information about ongoing studies of RFA (Mr MS Whiteley and T Rautio).

3.2 Inclusion/exclusion criteria

Clinical effectiveness studies were included in this review if they met the following

criteria:

- **Study design**: randomised controlled trials, quasi-randomised clinical trials, observational comparative studies, including cohort studies or case series. Individual case reports and duplicate publications in editorials and animal studies were excluded. Conference abstracts were not excluded.
- **Population:** patients with complicated varicose veins regardless of age, gender, risk factors or co-morbidity, or whether they have previously used interventions for treating varicose veins. Complications include venous incompetence (confirmed by Doppler or Duplex screening), oedema, venous ulceration, varicosity bleeding, changes in local skin colour, skin eczema and lipodermatosclerosis. Patients with uncomplicated varicose veins will be excluded.
- **Intervention**: Radiofrequency ablation (RFA) used as a single therapy, or in combination with other therapies.
- **Comparator:** conventional surgical therapies for varicose veins including stripping and/or ligatation, other surgical approaches or no comparator. Non-surgical interventions (e.g. drug, sclerotherapy, bandaging) were excluded.
- **Outcomes**:

  Primary outcomes: pain, quality of life or severe adverse events (i.e. mortality, deep vein thrombosis, pulmonary embolism)

Secondary outcomes: varicose vein recurrence, varicose vein re-operation, reflux recurrence, patient satisfactions, health care resource utilisation (e.g. time in hospital)

There was no exclusion on language.

Health economic studies were included for review on the basis of the following criteria:

- **Study design**: Any type of study.
- **Population**: As above for the effectiveness criteria
- **Intervention**: As above
- **Outcomes**: costs, cost consequence analysis, cost utility analysis or cost effectiveness analysis.

Two reviewers (YA, LN) independently scanned the titles and abstracts that were potentially relevant articles to be retrieved. In case of disagreement, the two reviewers met in order to reach a consensus.

3.3 Quality assessment

The quality of controlled studies was assessed in terms of methods of randomisation, adequacy of concealed allocation, blinding of outcome assessment, proportion of patients lost to follow up and scored overall using the Jadad scale.[25]

Several checklists have been suggested to assess the quality of case-series[26 27] These were considered by an internal methods group (see acknowledgements) to make an assessment of which checklist might be most appropriate to the type of included study envisaged, taking particular account of the nature of the problem being investigated. On this basis the generic framework suggested by the Cochrane Collaboration was felt to be most appropriate. This assesses openness to bias in four general areas:

- Selection bias
- Performance bias
- Detection bias
- Attrition bias

To these were added three further specific questions:

- Was the study prospectively conducted?
- Was the study a consecutive series?
- Were characteristics of the cases described prior to the intervention?

3.4 Data abstraction, reporting and analysis

Data was abstracted by (YA) and checked by another reviewer (JW) in a pre-defined proforma. Study quality was assessed by (YA).

Detailed tabular summaries of the characteristics (i.e. patients, intervention, comparator and outcomes) and methodological quality of all included studies were undertaken.

Given the relatively poor level of outcome reporting, variety of outcome domains and instruments used, and different durations of follow up across studies and the loss to follow up, quantitative pooling with meta-analysis was not employed.

4. Results

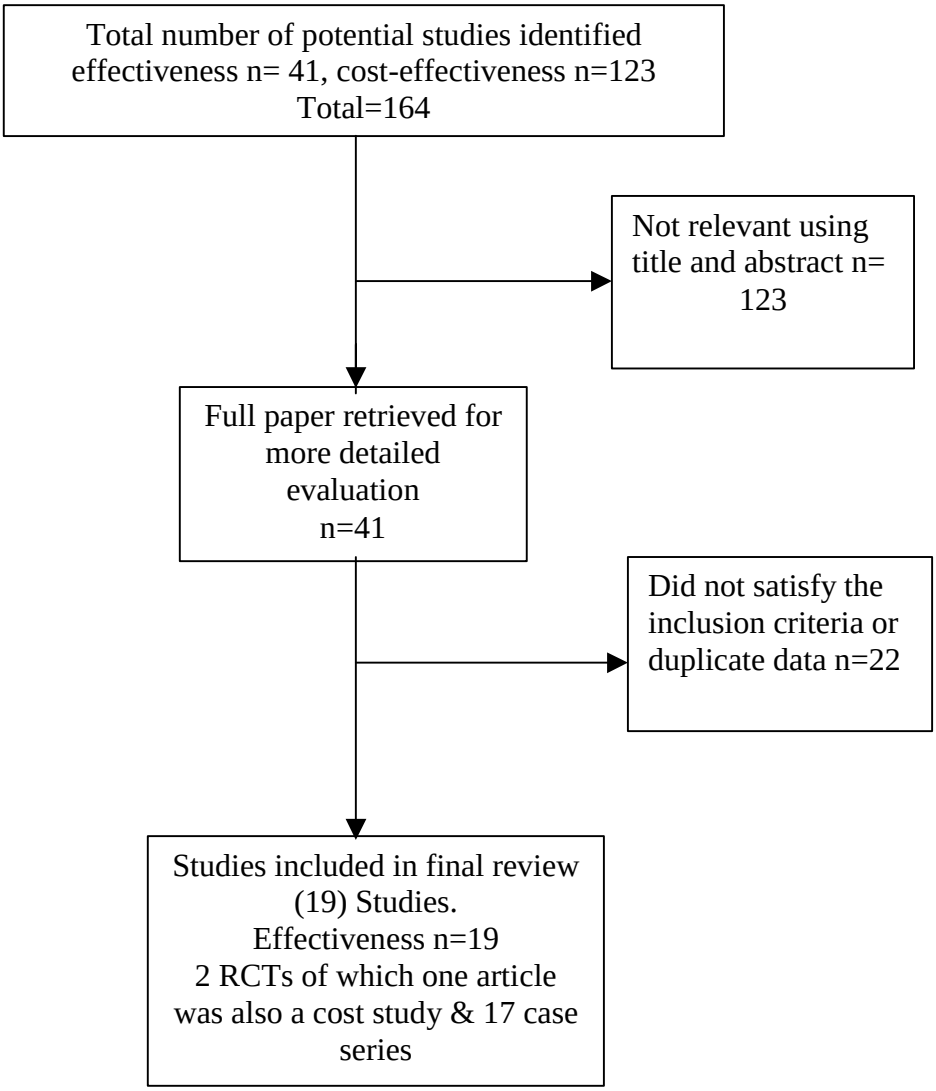
4.1 Quantity of evidence

A summary of the identified studies, excluded studies and included studies are summarised in the flow diagram below Figure (4). Inclusion/exclusion of the studies was carried out by two reviewers and Cohen's kappa (weighted by 1-abs(i-j)/(1-k)) (yes vs no =1; query vs no & query vs yes =0.5) showed Kappa = 90%
95% confidence interval for kappa = 76% to 100% , P < 0.0001

A total of two randomised controlled trials and 17 case series met the inclusion/exclusion criteria of this review. One cost study but no cost effectiveness study was identified by the searches. Figure 4

The citation details of excluded studies are provided in Appendix 4 and 5. Studies were rejected for reporting no clinical outcomes, being review articles or involving techniques other than treatment of varicose vein by RFA. Studies that were thought to be duplicate, were also excluded.

Figure 4 Summary of the included and excluded studies



4.2 Randomised controlled trials results

4.2.1 Study characteristics

The characteristics of the two included randomised controlled trials are summarised in

Table 5. Details of characteristics of trials can be found in appendix 8.

Table 5 Summary of characteristics of randomised controlled trials

	Rautio et al 2002 [28]	**Lurie et al 2003**[29]
Country	Finland	France, USA and Austria
Timing of study	2000	Not stated
Patient population	Patients were from *day case* surgery with *symptomatic*, previously *untreated* and uncomplicated GSV tributary varicosis and isolated *unilateral* saphenofemoral junction (SFJ) and GSV trunk *insufficiency*. Patients with coagulopathy or multiple, tortuous, larger diameter (>12 mm) trunks were excluded.	Patients had *symptomatic* varicose veins and GSV *incompetence*, confirmed with duplex ultrasound scanning who were candidates for conventional vein stripping with inclusion criteria of reverse flow in the GSV lasting longer than 0.5 seconds in the standing position, *age* between 21 and 80, CEAP *class* C2-C4, *ambulatory* status
RFA Mean age (years) **Sex (% female)** **(n= patients)**	33 years 93% F RFA (n=15)	49 years 74% F RFA (n=46 limbs) 45 patients
Comparator Mean age (years) **Sex (% female)** **(n= patients)**	38 years 92% F Conventional stripping surgery (n=13)	47 years 72% F Ligation & stripping surgery (n=40 limbs)
Outcome measures	Primary: a) Pain: Visual analogue pain scale VAS. 2) Quality of life using different scores: RAND-36, Decrease in venous disability. Secondary: reflux recurrence adverse events, and sick leave.	Primary: Pain & CIVIQ2 QoL. And adverse events Secondary: reflux recurrence and adverse events
Follow up period	7-8 weeks	72 hrs, 1 week, 3 weeks, and 4 months

The population of patients in (Rautio et al 2002) seems to be a highly selected group of patients of varicose veins. The age of the intervention group appears to be younger relative to the patients who had stripping surgery. In contrast, the population in (Lurie et al 2003) seems to include a wide range of classes CEAP C2-C4. The Rautio et al

2002 study had a shorter follow up compared with Lurie et al 2003. About 50 days, 4 months respectively.

4.2.2 Study quality

The quality of the trials are summarised in the Table 6. Detailed quality assessment in appendix 6 and 7.

Table 6 Summary of the randomised controlled trials quality

	Rautio et al 2002	**Lurie et al 2003**
Randomisation	Stated randomised but can't tell how it was carried out	Stated randomised but can't tell how it was carried out
Concealment	Adequate: sealed envelope	can't tell
Blinding	can't tell	can't tell
Loss to follow up	1/16 (6%) in RFA 4/17 (24%) Stripping	1/46 limbs (2%) in RFA 2/40 (5%) in S&L
Intention to treat analysis	Not stated	Not stated
Jadad score (see appendix 6 and 7)	2	1
Comments	- 85/121 consecutive patients scheduled were *excluded*. - This study seems to *exclude* difficult cases therefore external validity may be compromised - *Power* calculation to determine the sample size were not performed	-VNUS Medical Technologies provided *financial* support -Previous interventions for VV are considered among the *exclusion* criteria. - *Power* calculation to determine the sample size were not performed

4.2.3 Results of Effectiveness outcomes

Table 7 Summary of results - primary outcomes

	Rautio et al, 2002	**Lurie et al, 2003**
Pain	**VAS at rest on standing and on walking were significantly lower in RFA compared with stripping**. **Rest**: 0.7 (SD 0.5) v 1.7(SD 1.3) p=0.017 **Standing**: 1.3 (SD 0.7) v 2.6 (SD1.9), p=0.026 **Walking**: 1.8 (SD 0.8) v 3.0 (SD1.8, p=0.036) RFA group needed significantly less analgesics than stripping. P=0.004	**Difference in pain at 72 h compared S&L** Mean: -1.77 (SE 0.6) RFA v 2.9 (SE 0.7) S&L p<.0001 **Differences at 1 week follow up:** Mean: -2.4 (SE 0.6) RFA v 1.2 (SE 0.7) in S&L, p<.0001
Quality of life	Only bodily pain during the *first week* post operatively was statistically different (p=0.05) compared with the median baseline, RFA: Median: 23 (5-24) v 68 (68-90) Stripping: Median: 38 (20-45) v 68 (68-90)	**Difference in pain at 72 h:** Mean: -3 (SE 2.7) RFA v 13.3(SE 3.1) S&L, p<.0001 **Difference at 1 week follow up** RFA: -9.2, SD: Control: 3.7. SD: (P<0.001)

The pain was measured in Rautio et al, 2002[28] relative to stripping using VAS but Lurie et al, 2003[29] measured the difference in pain i.e. relative to before treatment.

Table 8 Summary of results - Secondary outcomes.

	Rautio et al, 2002	Lurie et al, 2003
Reflux free assessment	15/15 (100%) v 12/13 (92%) NS	42/44 limbs RFA (95%) v 34/34 (100%) S&L NS
Days to return to work	6.5 (SD 3.3) days v 15.6 (SD 6.0) days p<.001	4.7 days v 12.4 p<.01
Recurrence of varicose veins	Not reported	Not reported
Patient satisfaction	1/15 (7%) RFA v 4/13 (31%) stripping were not satisfied with the cosmetic outcome	Not stated

(NS): Not statistically significant

There was a statistically significant difference in the days to return to work in favour of RFA in both the two RCTs above. However no difference was found in both RCTs for the reflux free status. Recurrence of varicose veins was not reported in either of the RCTs above.

4.2.4 Adverse events reported in RCTs

Table 9 Summary of adverse events.

	Rautio et al, 2002	Lurie et al, 2003
Mortality	Not reported	Not reported
Pulmonary embolism	Not reported	Not reported
Complications	-Paresthesia RFA 2/15 (13%) v 3/13(23%) stripping NS - thrombophlebitis RFA 3/15 (20%) v 0/13 stripping NS -hematoma RFA 1/15 (7%) RFA v 4/13 (31%) stripping NS - skin injuries RFA 1/15(7%) v 0/13 stripping NS	- Complications were statically significant (in favour of RFA) at 72 h, 1 week and 3 weeks for: *ecchymosis* and *haematoma* and for *tenderness* in 72 hours only

(NS): Not statistically significant

The complications in both studies were more annoying than serious. In Rautio et al there were a few minor adverse events that did not show a statistical differences between RFA ant stripping but in Lurie et al study there were statistically different events up to three weeks in terms of *ecchymosis*, *haematoma* and tenderness in 72 hours only.

4.3 Case series results of effectiveness:

17 case series met the inclusion criteria for this review. Study characteristics, quality and results will be stated in this section. Further details are in appendices 6,7 and 8.

Case series can provide longer follow up than RCTs. Data about safety aspects of the intervention can be obtained. The quality of case series in terms of selection bias, loss to follow up and of course, the non-existence of a control may all limit the information taken from case series. The total number of patients included in the 17 case series was 2,266, however the information from the VNUS stated that RFA was carried out well above 30,000 worldwide at the beginning of 2004.

4.3.1 Study characteristic of included case series studies

An overview of the characteristics of the results of the included case series is shown in table 10.

Table 10 Study characteristics of included case series studies

Characteristic [number of studies]	**Median (range) value**	**n=(%) Percentage of reporting**
Population of complicated varicose veins or documented venous incompetence	-	17/17 All of the included studies met this definition
Age years stated in [n=9]	47 (42-51) years	
Sex stated [n=13]	76 % female (63-100) %	
Number of patients [16]	68 (10-490) patients (not legs)	
Year of study publication	2002 (1999-2004)	
RFA intervention alone	-	4/17 studies reported another surgical treatment given with RFA, in the remaining 15/17 studies can't tell for sure.
Duration of follow up of the last assessment carried forward	12 months (6-37)	The long follow up had a significant loss to follow up.
Country USA & Canada Europe Europe & USA		 6/17 (35%) 10/17 (59%) 1/17 (6%)
Primary outcomes reported Pain QoL Serious adverse events (mortality, DVT, PE)		 6/17 (35%) 0/17 (0%) 3/17 (18%)
Secondary outcomes reported Varicose vein recurrence Re-operation Reflux recurrence Patient satisfactions Hospital stay		 10/17 (59%) 0/17 (0%) 17/17 (100%) 5/17 (29%) 0/17 (0%)

The median age of the individuals in case series was 47 years and this would represent people in the middle age i.e. not elderly. Majority were females. The Year of publication of case series started in 1999 at the time the device was given clearance from the licensing authorities, CE Mark approval, in 1998 and USA FDA clearance as well as Australian approval allowing registry studies in the three countries. In 13/17 (76%) the RFA was the intervention given but there were 5/17 (29%) studies that there was an adjuvant surgical treatment given either previously in one study or concurrently in the other four.
The duration of the follow up varied between the studies but the median follow up was 12 months.

4.3.2 Quality of case series

Quality of included cases series is tabulated in table 11 and further details are in appendix 9.
The table below shows the quality of case series studies according to criteria of dealing with biases that may occur when the studies are conducted. Only one study was reported to have consecutive patients and only one was a prospective case series. None of the studies stated that a different assessor than the operating surgeon carried out assessment. The validity of measures stated was not discussed in any of the studies.

Table 11 Quality of case series included in this study N=17

Type of bias and if anything was done to reduce it	Number of case series that stated taking action to reduce bias (%)
Selection bias Consecutive	1/17 (6%) stated consecutive patient followed up, the rest of case series did not state this. Therefore it could be a bad reporting rather than the patients were non-consecutive.
Performance bias Absence of co-intervention	4/17 stated there were adjuvant treatment to RFA, the rest did not report other treatment
Detection bias -Prospective or before and after -Blinding of - independent assessor -Validated measures used stated in the study	- 1/17 (6%) stated specifically as prospective - 0/17 - 0/17 -0/17
Attrition bias Loss to follow up less or equal to 20%	11/17 (65%)

There was a large loss to follow up in 65% of the studies. The results were stated in those who were available to follow up i.e. in completers of the treatment.
The table below clearly shows the pain was not assessed in a way that results would be related to the intervention. Drug treatments as pain killer postoperatively were not stated. And all studies for pain had a large rate of loss to follow up.

Table 12 Case series stated pain as an outcome

Study	Pain reported as	Comments
Dauplaise and Weiss 2001	251 patients (79%) pre treatment to 8 (8%) following the intervention	Huge loss to follow up at 6 months
Goldman and Amiry 2002	Reported as: complete elimination of leg pain	Assessment at the postoperative period
Merchant et al 2002	83% with pain before, to 3,3%after	At 2 years
Weiss and Weiss 2002	119 (85%) before, 1(5%) after the intervention	Huge loss to follow up at 2 years
Manfrini *et al* 2000	75% with pain pre-treatment to 5% after	At 6 months (data taken from a graph)
Chandler et al 2000	74% with pain before 5% after	At I year (data taken from a graph)

Table 13 Case series stated recurrence of varicose veins

Study	Recurrence or recanalisation rate	Comments
Rosenblatt 2003 Abstract only	4.3% had recanalisation	At 12 months
Goldman and Amiry 2002	7% recurrence of veins	At 6 months
Merchant et al 2002 USA	8% recurrence	At 2 years
(a) Fassiadis *et al* 2002	Stated as no evidence of recanalisation	-
Sybrandy and Wittens 2002.	11.5 % recurrence	-
(b) Fassiadis *et al* 2002	2/12 (16%)	-
Rautio *et al* 2002 Finland Feasibility study	27% recanalisation	At 10 months
Mulkens 2003 Germany Abstract only	No evidence of recurrence at 3 years	Huge loss to follow up
Dauplaise and Weiss 2001	5.4% recurrence	At 6 months
Weiss and Weiss 2002	10% recurrence	At 2 years

The recurrence rate varied between studies (0% to 27%) so did the follow up (6 months to two years).

Table 14 Case series stated recurrence of reflux

Study	Reflux recurrence investigated by scanning	Comments
Whiteley *et al* 2003[30]	0%	9/9 only were available for assessment of 750 legs had RFA at 2 years
Rosenblatt 2003[31]	4%	Mean follow up 3.4 months
Dauplaise and Weiss 2001[32]	5%%	6 months
Goldman and Amiry 2002[33]	10%	Postoperative period
Merchant et al 2002[34]	15%	12 months
Weiss and Weiss 2002[35]	2%	At 1 week
(a) Fassiadis *et al* 2002[36]	No evidence of reflux	One year
Sybrandy and Wittens 2002[37] Netherlands.	12%	1 year
(b) Fassiadis *et al* 2002[38]	2/12 (17%)	Not stated the assessment time
Rautio *et al* 2002[39] Feasibility study	27%	At 9 months
Pichot *et al* 2000[40]	0%	6 months
Mulkens 2003[41] Abstract only	10%	2 years
Fassiadis *et al* 2003[42]	0%	
Manfrini etal 1999[43] Abstract Abstract only	10%	6 months
Pichot *et al* 2004[44]	10%	2 years
Manfrini *et al* 2000[45]	4%	6 months
Chandler et al 2000[46]	3.8%	Mean follow up 4.9 months

The recurrence of reflux varied following RFA between 0% and 27%. The follow up for the assessment of reflux ranges from postoperatively and up to 2 years.

Table 15 Case series stated satisfaction

Study	Satisfaction in terms of recommending RFA to a friend
Dauplaise and Weiss 2001	Yes 94% will recommend
Goldman and Amiry 2002	Yes 100% will recommend
Merchant et al 2002	Yes 96 % will recommend
Weiss and Weiss 2002	Yes 98% will recommend
Mulkens 2003 Abstract only	Yes 95% will recommend

Patients were asked if they recommend RFA to a friend and the response was clearly favourable in the 5 studies that reported this recommendation.

Table 16 Adverse events in case series of RFA

Study	Mild (%)	Severe (%)
Rosenblatt 2003	Paresthesia 11% Burns 1.4%	-
Dauplaise and Weiss 2001	Burns 2.8% Clinical thrombophlebitis 3.1%	DVT 3/ 288 (1%)
Chandler et al 2000	Paresthesia 19% Skin burns 2.7% Clinical thrombophlebitis 6.7%	
Weiss and Weiss 2002	Paresthesia 1%	DVT 1%
Rautio *et al* 2002 Feasibility study	Paresthesia 10%. Burns 3.3%	
Merchant et al 2002	Paresthesia 15% Thronbophlebitis 2% Burns 4.2%	DVT 3/286 (1%)
Mulkens 2003 Conference abstract	Thronbophlebitis 3.7% Paresthesia 14%	PE 1/323 (0.3%)

While the reported rate of DVT in three different studies was about 1%, less mild adverse events were mainly paresthesia (up to 15%), skin burns (up to 4.2%) and thrombophlebitis in up to 6.7%.

4.4 Cost and cost effectiveness of RFA

The searches of this review identified one RCT study examining the costs of RFA as part of the trial (Rautio et al, 2002). No formal economic evaluation (i.e. aggregated assessment of costs and health benefits) of the use of RFA for varicose vein patients was found.

The purpose of this section is to combine current clinical outcome and cost data in order to estimate the potential cost effectiveness of RFA relative to conventional surgical approaches. In addition, if RFA were to be introduced into NHS practice, a potential budget impact has been calculated for West Midlands region.

4.4.1 Methods

This economic analysis was undertaken from a healthcare perspective and assesses the cost effectiveness of RFA compared to stripping in varicose vein patients as an incremental cost per quality cost per quality adjusted life year (QALY).

Assessment of health benefits
To minimise bias, it was intended that health benefits associated with RFA be sourced from RCT evidence only. Both RCTs assessed quality of life, Rautio et al (2002) using the generic measure, SF-36 and Lurie et al (2003) using a disease specific measure, CIVIQ2 (see Table 7). Neither study directly assessed utility. A method of imputing utility from SF-36 scores is available. However, this requires individual patient data that was not available in this situation [1].
Estimates of the patient utility were imputed from pain VAS scores. Kovacs and colleagues (2004)[2] recently published a survey where they have examined the relationship between VAS pain and utility (as assessed by the EQ-5D) in patients with low back pain. Using regression methods they found that a 1mm increase in VAS (on a 0-100 scale) is associated with a -0.035 decrement in utility. Although, collected in a different population group, for the purposes of this analysis it was assumed that the relationship held for varicose vein patients.
Although, there appeared to be some difference in the short-term complications associated with RFA and stripping (see Table 9), these differences were small and the balance of complications appeared equivalent across both groups. It was therefore assumed that any disutility (and costs) associated with short-term complications was equivalent between RFA and stripping. Furthermore, as there is there is currently insufficient data on the comparative rate of longer-term complications (e.g. deep vein thrombosis, pulmonary embolisms) and recurrence rates with RFA and stripping, these were assumed to the same across the two procedures.

Assessment of costs
The healthcare costs of RFA and stripping were derived from the costing analysis reported in RCT of Rautio et al (2002). US dollars at 2000 prices were converted to UK pounds at 2004 prices, based on both purchasing parity power and European (EU-15) healthcare price inflation rates.

Assessment of cost effectiveness
It was assumed that the probability of survival was equivalent for RFA and stripping. Therefore, the incremental cost per QALY of RFA compared to conventional surgical

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[1] Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 health survey. *J Clin Epidemiol* 1998;51:1115-28

[2] Kovacs,F.M.; Abraira,V.; Zamora,J.; Teresa Gil,del Real; Llobera,J.; Fernandez,C. et al. Correlation between pain, disability, and quality of life in patients with common low back pain. *Spine* 2004;**29**:206-210.

approaches was driven by differences in healthcare costs and utility (quality of life) gain.

Assessment of budget impact

The number of the NHS varicose vein procedures (electives) in the West Midland Government Office Region, based on OPCS-4 codes (L85 - Ligation of varicose vein of leg & L87 - Other operations on varicose vein of leg) was obtained from HES2 for the year 2002/2003. The additional healthcare cost of RFA was obtained as outlined above.

4.4.2 Results

Assessment of health benefits

Utility values were imputed using the pain VAS scores reported by Rautio et al (2002) (see Table 7).

Table 17 Imputation of utility values

	Pain VAS at 2-wks* Mean (SD)	Incremental Pain VAS at 2-wks Mean (SD)	Incremental utility at 2-wks Mean (SD)
RFA	12.7 (6.8)	11.6 (20.1)	0.41 (0.70)
Stripping	24.3 (28.5)		

*: Weighted across pain VAS scores at rest, standing and walking expressed on a 0-100 scale

Thus the average gain in utility at 2-weeks with RFA relative to stripping was determined to be 0.41

Assessment of costs

The various healthcare costs associated with RFA and stripping are summarised in the table below. It can be seen that the majority of the additional cost of RFA is the cost of the closure catheter.

This additional cost of RFA of $533 at 2000 prices corresponds to £380 at 2004 prices. This difference in cost, corresponds with the current European list price of the RFA catheter of 500 Euros (£312) to 600 Euros (£375) (VNUS Medical Technology, Mr Farley President and Chief Executive Officer, personal communication September 2004).

Table 18 Healthcare costs of stripping and RFA (US$ at 2000 prices) at 2-weeks follow up

	Stripping		RFA	
	Units & unit price	**Total**	**Units & unit price**	**Total**
Generator	0	0	1/$14.54	14.54
Annual costs		0		3.36
Surgeon	99 min/$32	53	115 min/$32	61
Radiologist	0	0	75 min/$32	40
Operating room	99 min/$73	121	115 min/$73	140
Anaesthesia & recovery room	1/$72	72	1/$72	72
Basic instrumentation	1/$50	50	1/$50	50
Closure catheter	0	0	1/$446	446
US equipment rent	0	0	1/$31	31
Follow up	6/13 patients/$62	29	1/15 patients/$62	4
Analgesic medication	1.3 tabs 14 days/$0.3	6	0.4 tabs 14 days/$0.3	
Total		**331**		**864**

Adapted from Rautio et al (2000)

Although not formally included in this economic evaluation, the indirect costs associated with earlier return to work were $607 with RFA and $1,566 with stripping. This cost saving outweighs the increased healthcare costs associated with RFA.

Assessment of cost effectiveness

Using the differences in costs and utility calculated above, an incremental cost per QALY was derived Table 19.

Table 19 Incremental cost per QALY of RFA compared to Stripping

	Incremental utility* Mean (95% CI)	**Incremental cost**	**Incremental cost per QALY* Mean (95% CI+)**
RFA vs Stripping	0.016 (0.006 to 0.027)	£380	£23,750 (£14,074 to £63,333)

*Assuming utility gain over 1-year is totally derived during the first 2-weeks follow up

+: pseudo 95% CI as no within subject estimate of the variance in incremental cost

Assessment of budget impact

It is estimated that the number of varicose vein procedures (electives) in the NHS in West Midlands Government Office Region for 2002/2003 was 17,401. The NHS Reference Costs 2003 and National Tariff 2004[47] ('Payment by Results Core Tools 2004') for the cost of surgical treatment was £752. Thus the total budget impact of varicose veins to the West Midlands is some £13 million per annum.

If RFA were to be introduced as a replacement for conventional surgery approaches, it is estimated that the additional cost would be £380.

The selection criteria for patients receiving RFA in RCTs has been restricted to those symptomatic patients who are not advanced cases (see Table 5). If it were assumed that 50% of cases were severe then it is estimated that RFA would be applied to 8,700 cases in the West Midlands at an additional budget impact of some £3 million per annum.

5. Discussion

Surgical removal of saphenous vein (stripping and ligation) is the current conventional treatment for patients with varicose veins. It does however cause postoperative morbidity and a psychological burden. Radiofrequency ablation (RFA) of the saphenous vein results in obliteration of the vein lumen; therefore, RFA has been introduced to provide an alternative to traditional surgical therapy.

The purpose of this review was to assess the clinical and cost effectiveness of RFA for the treatment of varicose veins. The primary outcomes that were thought important were pain, quality of life or severe adverse events (i.e. mortality, deep vein thrombosis, pulmonary embolism).

Summary of clinical benefits:

The literature searches for this review identified two RCTs and 17 case series that met the inclusion criteria. The comparators in the two RCTs were different, stripping in one, stripping and ligation in the second. Pain in Rautio et al was significantly improved in RFA at one week postoperatively using QoL index RAND-36 when compared with stripping. In the EVOLVeS trial at one week follow up- improvement of pain score was significant compared before the treatment. The number of days to return to work was significantly shorter in both studies in favour of the RFA. Return to normal activities was also significantly shorter in the EVOLVeS trial.

There was no difference in the absence of reflux and the total number of postoperative adverse events in both trials when compared with conventional surgery. However, in the EVOLVeS trial, adverse effects were significantly less in RFA, up to three weeks follow up for particular adverse events: ecchymosis, haematoma, and less for tenderness up to 72 hours. Severe adverse events i.e. mortality, DVT and PE were not reported in either of the trials.

Quality: The RCTs were not judged to be of a high quality. There were no details about how randomisation was carried out. They were not analysed according to ITT and blinding the assessor were not carried out. No sample size calculation was reported in either and they were for a short term follow ups only, 50 days and 4 months.

The population of the two RCTs where highly selected to allow generalisability to different population in other centres.

Six case series studies reported pain as one of the outcomes. The index to measure pain is not the same in all studies. In Dauplaise and Weiss, leg pain was reported in 251/316 (79%) prior to treatment but was only reported in 8/93 (8.6%) patients available for assessment. Goldman and Amiry reported complete elimination of pain but did not state at what time after the RFA. Merchant et al, at 2 years assessment, reported the proportion of patients with pain dropped from 265/319 (83%) pre-treatment to just 4/121(3 %) for patients with complete occlusion.

In Weiss and Weiss leg pain was reported in 119/140 in pre-treatment but at two years follow up, pain was reported in 1/21 (5%). Manfrini et al 2000, reported pain in 72% but at 12-month assessment pain was reported in 5% of patients but there was an adjunctive prior or concurrent to RFA. Chandler et al 2000 reported 74% of 91 patients had pain pre-treatment but at one year assessment only (5%) of 19 patients had pain.

Ten case series studies reported rate of recurrence of varicose veins between 0% and 27%. The follow up time was different and there was a huge loss to follow 65% had loss to follow up more that 20%.

Satisfaction to recommend RFA from those who had this intervention was very high (94%-100), however, if people who had RFA were the type of patients selected to be of low severity, then recommendation would only apply to people who have similar severity of disease.

All case series as well as the two included RCTs reported improvements related to recurrence rate of reflux following RFA. Duplex ultrasonography may not distinguish patients with the symptoms and signs of different grades of chronic venous insufficiency[48] with the same accuracy as for ambulatory venous pressure measurement which is long thought to represent the gold standard. Furthermore, duplex ultrasonography may not be able to distinguish post thrombotic from primary deep venous incompetence as accurately as phlebography.[49]

Summary of adverse events:

RCT studies did not show differences in complication rates in RFA and stripping of S&L. For case series of longer follow up than RCTs studies skin burns occurred in 4.2% and paresthesia occurred in 0-15 % of patients clinical thrombophlebitis in up to 6.7%.

Two studies reported DVT rate of 3/ 288 (1%) and 3/286 (1%) one of these reports also reported one case of PE in case series 0.3%, which was not fatal. The number of cases of DVT is too small to allow a meaningful comparison with DVT rates following conventional surgery, which were reported to be 0.2%- 1.8%. It is not known if the difference in rate is explained in the selection of patients, due to the procedure, the skills needed or indeed a chance finding due to small number of cases found.

It was surprising to identify only one cost study for RFA. An ongoing HTA project will assess the cost effectiveness of the commonly used treatments for varicose veins by way of Markov process decision model. The data for the modelling will be obtained through a combination of systematic literature reviews and the collection of retrospective and prospective data on patients undergoing treatment for varicose veins. This will include randomised controlled studies in three sub-groups of patients in whom conservative treatment, sclerotherapy and surgery will be compared. The model will allow an assessment of the incremental cost effectiveness of each treatment modality in sub groups of patients based upon their symptomatic,

investigative and demographic features. Patient and societal priorities for treatment will be assessed using a "willingness to pay" (WTP) technique.
(Publication date June 2005) http://www.ncchta.org/project.asp?PjtId=1064

The strengths of the review come from the comprehensive search and its systematic review of the evidence about effectiveness and cost of RFA in the included studies.

The limitations of the review are related to the quality of available evidence about the objective use of RFA for the treatment of varicose veins particularly details of randomisation and the length of follow up. On the other hand, case series quality was compromised by assessing the effect on patients who only completed the study as well as the selection bias of cases treated with RFA. It is possible that publication bias in favour of a positive result may have occurred and studies with negative results may not have been published.

Cost effectiveness

The results of this economic evaluation indicate RFA to be a potentially attractive cost effective (i.e. incremental cost effectiveness ratio of £30,000 or less per QALY) alternative to conventional surgical treatment for varicose veins.
However, the results of this analysis are intended to be indicative rather than definitive and need to be interpreted with considerable caution. This economic analysis was based on short-term data (2-week) from a relatively poor quality RCT (Table 7) and based on a number of assumptions, particularly the estimation of utility gain. Furthermore, given the lack of comparative long-term outcome data, this analysis was unable to take into account potential differences in long-term complications and recurrence rates.

It would take only relatively small increases in morbidity (e.g. DVT or PE) with RFA to reduce its acceptability, safety and, therefore, the potential cost effectiveness, as an alternative to conventional surgical approaches. The review of case series evidence in this report (Table 16) showed the rate of symptomatic and duplex ascertained DVT is about 1% following RFA. The literature of incidence rate of DVT following stripping varied across studies from 0.2% to 1.8%.
Therefore, future research needs to focus in providing unbiased estimates of the relative long-term effects of RFA in comparison to conventional surgical approaches for varicose veins.

Further research

This review has identified a number of future research priorities:

- Further adequately powered and well-conducted RCTs with long-term follow up[3].
- An independent register for collection of adverse events following treatment with RFA and conventional surgical approaches for varicose veins.
- Incorporation of long-term outcomes within a cost effectiveness study

Conclusion

This systematic review of RFA in the treatment of varicose identified two-short term RCTs and 17 cases series. Compared with both stripping alone and stripping plus ligation, RFA was associated with a reduction in post-operative pain relief at 2-weeks and no significant difference in adverse events. The long-term safety of RFA is supported by evidence from a number of case series of up to 2 years post-operative follow up, and these results were from non-comparative studies which were prone to substantial attrition bias. Based on improvements in short-term pain relief, an indicative economic analysis demonstrates that RFA may be a cost effective alternative to conventional surgical therapy for varicose veins. RFA is not available on the NHS in the UK and those studies of patients who have had RFA may be a selected group of patients usually of higher economic status who are looking for a quick yet cosmetically pleasing answer to their problem. It may also explain why some of the patients are more willing to get back to work as soon as possible. These findings require confirmation from future studies providing unbiased estimates of the relative long-term effects of RFA in comparison to conventional surgical approaches for varicose veins.

[3] There is an ongoing trial (registered with National Research Register NRR) 'Randomised single blind patient controlled trial of VNUS closure compared with groin dissection and LSV stripping for recurrent varicose veins' Trial expected to report in 2008.

6. Appendices

Appendix 1 Search strategy for effectiveness studies

Database: Ovid MEDLINE(R) <1966 to January Week 2 2004>
Search Strategy:
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1 (radiofrequency adj ablation).mp. [mp=title, abstract, name of substance, mesh subject heading] (1878)
2 (catheter adj ablation).mp. [mp=title, abstract, name of substance, mesh subject heading] (2581)
3 exp CATHETER ABLATION/ (5611)
4 vnus.mp. (8)
5 (venus adj closure).mp. [mp=title, abstract, name of substance, mesh subject heading] (0)
6 venus.mp. (232)
7 (endovenous adj obliteration).mp. [mp=title, abstract, name of substance, mesh subject heading] (5)
8 or/1-7 (6752)
9 exp varicose veins/ or exp venous insufficiency/ or exp saphenous vein/ (20320)
10 (varicose adj ulcer$).mp. (199)
11 (saphenous adj vein$).mp. (7778)
12 (venous adj insufficienc$).mp. (2074)
13 or/9-12 (23344)
14 8 and 13 (29)
15 randomized controlled trial.pt. (182651)
16 controlled clinical trial.pt. (65169)
17 randomized controlled trials.sh. (30142)
18 random allocation.sh. (49464)
19 double blind method.sh. (75864)
20 single-blind method.sh. (7701)
21 or/15-20 (308710)
22 (animals not human).sh. (2840980)
23 21 not 22 (308710)
24 clinical trial.pt. (370735)
25 exp clinical trials/ (148780)
26 (clin$ adj25 trial$).ti,ab. (94604)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (74963)
28 placebos.sh. (22537)
29 placebo$.ti,ab. (81050)
30 random$.ti,ab. (271226)
31 research design.sh. (36630)
32 or/24-31 (645719)
33 32 not 22 (645719)
34 33 not 23 (354899)
35 comparative study.sh. (1076950)
36 exp evaluation studies/ (470362)
37 follow up studies.sh. (276006)
38 prospective studies.sh. (166636)
39 (control$ or prospectiv$ or volunteer$).ti,ab. (1378007)

40 or/35-39 (2770220)
41 40 not 22 (2770220)
42 41 not (23 or 34) (2323696)
43 23 or 34 or 42 (2987305)
44 43 and 14 (21)
45 from 44 keep 1-21 (21)

Database: EMBASE <1980 to 2004 Week 04>
Search Strategy:

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1 (radiofrequency adj ablation).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1748)
2 (catheter adj ablation).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (2393)
3 vnus.mp. (11)
4 (venus adj closure).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (0)
5 intravenous catheter.mp. or exp Intravenous Catheter/ (1568)
6 (endovenous adj3 obliteration).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (4)
7 exp VARICOSIS/ or exp LEG VARICOSIS/ or varicosis.mp. (12346)
8 (varicose adj vein$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1914)
9 exp Chronic Vein Insufficiency/ or exp Saphenous Vein/ (4629)
10 (saphenous adj vein$).mp. (6235)
11 (venous adj insufficienc$).mp. (1891)
12 (varicose adj ulcer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (86)
13 or/1-6 (5289)
14 or/7-12 (20554)
15 13 and 14 (45)
16 randomized controlled trial/ (81056)
17 exp clinical trial/ (293583)
18 exp controlled study/ (1690023)
19 double blind procedure/ (50342)
20 randomization/ (8847)
21 placebo/ (67253)
22 single blind procedure/ (4537)
23 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (105222)
24 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (70151)
25 (placebo$ or matched communities or matched schools or matched populations).mp. (109390)
26 (comparison group$ or control group$).mp. (105748)
27 (clinical trial$ or random$).mp. (483729)
28 (quasiexperimental or quasi experimental or pseudo experimental).mp. (953)
29 matched pairs.mp. (1519)
30 or/16-29 (2035159)
31 15 and 30 (16)
32 from 31 keep 1-16 (16)

Database: CINAHL <1982 to December Week 2 2003>
Search Strategy:
---
1 radiofrequency ablation.mp. (60)
2 catheter ablation.mp. or exp Catheter Ablation/ (288)
3 vnus.tw. (0)
4 venus closure.tw. (0)
5 venus.mp. (16)
6 (endovenous adj obliteration).mp. [mp=title, cinahl subject headings, abstract, instrumentation] (0)
7 or/1-6 (318)
8 varicose vein$.mp. or exp Varicose Veins/ (670)
9 venous insufficiency.mp. or exp Venous Insufficiency/ (259)
10 saphenous vein$.mp. or exp Saphenous Vein/ (113)
11 (varicose adj ulcer$).mp. [mp=title, cinahl subject headings, abstract, instrumentation] (4)
12 exp Venous Ulcer/ (515)
13 venous insufficienc$.tw. (97)
14 or/8-13 (960)
15 7 and 14 (0)
16 from 14 keep 1-10 (10)

Database: Chochrane Library 2004 Issue 3 DARE and NHS EED
#1 (radiofrequency next ablation)
#2 vnus
#3 (venus next closure)
#4 (endovenous next obliteration)
#5 (#1 or #2 or #3 or #4)
#6 (varicose next vein*)
#7 VARICOSE VEINS
#8 (varicose next ulcer*)
#9 (venous next insufficiency)
#10 VENOUS INSUFFICIENCY
#11 (saphenous next vein*)
#12 SAPHENOUS VEIN
#13 (#6 or #7 or #8 or #9 or #10 or #11 or #12)
#14 (#5 and #13)

Appendix 2 Search strategy for economic evaluation, modelling and quality of life

Database: Ovid MEDLINE(R) <1966 to January Week 2 2004>
Search Strategy:

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1 economics/ (23710)
2 exp "costs and cost analysis"/ (106315)
3 cost of illness/ (5612)
4 exp health care costs/ (20965)
5 economic value of life/ (4175)
6 exp economics medical/ (9416)
7 exp economics hospital/ (12538)
8 economics pharmaceutical/ (1273)
9 exp "fees and charges"/ (20312)
10 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (183065)
11 (expenditure$ not energy).tw. (7985)
12 (value adj1 money).tw. (327)
13 budget$.tw. (8380)
14 or/1-13 (280846)
15 (radiofrequency adj ablation).mp. [mp=title, abstract, name of substance, mesh subject heading] (1878)
16 (catheter adj ablation).mp. [mp=title, abstract, name of substance, mesh subject heading] (2581)
17 exp CATHETER ABLATION/ (5611)
18 vnus.mp. (8)
19 (venus adj closure).mp. [mp=title, abstract, name of substance, mesh subject heading] (0)
20 venus.mp. (232)
21 (endovenous adj obliteration).mp. [mp=title, abstract, name of substance, mesh subject heading] (5)
22 exp varicose veins/ or exp venous insufficiency/ or exp saphenous vein/ (20320)
23 (varicose adj ulcer$).mp. [mp=title, abstract, name of substance, mesh subject heading] (199)
24 (saphenous adj vein$).mp. (7778)
25 (venous adj insufficienc$).mp. (2074)
26 or/22-25 (23344)
27 or/15-21 (6752)
28 26 and 27 (29)
29 14 and 28 (1)
30 from 29 keep 1 (1)

Database: EMBASE <1980 to 2004 Week 04>
Search Strategy:

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1 cost benefit analysis/ (17166)
2 cost effectiveness analysis/ (31987)
3 cost minimization analysis/ (607)
4 cost utility analysis/ (964)
5 economic evaluation/ (1725)
6 (cost or costs or costed or costly or costing).tw. (108193)
7 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (50882)
8 (technology adj assessment$).tw. (1029)
9 or/1-8 (161562)
10 (radiofrequency adj ablation).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1748)
11 (catheter adj ablation).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (2393)
12 vnus.mp. (11)
13 (venus adj closure).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (0)
14 intravenous catheter.mp. or exp Intravenous Catheter/ (1568)
15 (endovenous adj3 obliteration).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (4)
16 exp VARICOSIS/ or exp LEG VARICOSIS/ or varicosis.mp. (12346)
17 (varicose adj vein$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1914)
18 exp Chronic Vein Insufficiency/ or exp Saphenous Vein/ (4629)
19 (saphenous adj vein$).mp. (6235)
20 (venous adj insufficienc$).mp. (1891)
21 (varicose adj ulcer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (86)
22 or/16-21 (20554)
23 or/10-15 (5289)
24 22 and 23 (45)
25 9 and 24 (2)
26 from 25 keep 1-2 (2)

OHE HEED April 2004
Terms used:
Endovenous obliteration
Radiofrequency ablation
Vnus
Venous and Varicose

Database: Modelling Ovid MEDLINE(R) <1966 to January Week 3 2004>
Search Strategy:

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1 exp varicose veins/ or exp venous insufficiency/ or exp saphenous vein/ (20335)
2 (varicose adj ulcer$).mp. (201)
3 (saphenous adj vein$).mp. (7789)
4 (venous adj insufficienc$).mp. (2078)
5 varicose vein$.mp. (8079)
6 or/1-5 (23801)
7 decision support techniques/ (4361)
8 markov.mp. (2526)
9 exp models economic/ (3568)
10 decision analysis.mp. (1864)
11 cost benefit analysis/ (32046)
12 or/7-11 (40720)
13 6 and 12 (59)
14 from 13 keep 1-59 (59)

Database: quality of life Ovid MEDLINE(R) <1966 to January Week 3 2004>
Search Strategy:

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1 exp varicose veins/ or exp venous insufficiency/ or exp saphenous vein/ (20335)
2 (varicose adj ulcer$).mp. (201)
3 (saphenous adj vein$).mp. (7789)
4 (venous adj insufficienc$).mp. (2078)
5 varicose vein$.mp. (8079)
6 or/1-5 (23801)
7 quality of life/ (38895)
8 life style/ (18812)
9 health status/ (22498)
10 health status indicators/ (7868)
11 or/7-10 (81103)
12 6 and 11 (125)
13 from 12 keep 1-125 (125)

Appendix 3 The included studies

1. Chandler JG, Pichot O, Sessa C, Schuller-Petrovic S, Kabnick LS, Bergan JJ. Treatment of primary venous insufficiency by endovenous saphenous vein obliteration. *Vascular Surgery* 2000;**34**:201-14.

2. Dauplaise TL,.Weiss RA. Duplex-guided endovascular occlusion of refluxing saphenous veins. *Journal of Vascular Technology.* 2001;**25**:79-82.

3. Fassiadis N, Holdstock JM, Whiteley MS. Endoluminal radiofrequency ablation of the long saphenous vein (VNUS closure) - a minimally invasive management of varicose veins. *Minimally Invasive Therapy & Allied Technologies* 2003;**12**:91-4.

4. Fassiadis N, Kianifard B, Holdstock JM, Whiteley MS. A novel approach to the treatment of recurrent varicose veins. *Int Angiol* 2002;**21**:275-6.

5. Fassiadis N, Kianifard B, Holdstock JM, Whiteley MS. Ultrasound changes at the saphenofemoral junction and in the long saphenous vein during the first year after VNUS closure. *Int Angiol* 2002;**21**:272-4.

6. Goldman MP,.Amiry S. Closure of the greater saphenous vein with endoluminal radiofrequency thermal heating of the vein wall in combination with ambulatory phlebectomy: 50 patients with more than 6-month follow-up. *Dermatol Surg* 2002;**28**:29-31.

7. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O *et al*. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). *J Vasc.Surg* 2003;**38**:207-14.

8. Manfrini S, Gasbarro V, Cataldi A, Occhionorelli S, Cerreta G, Galeotti R *et al*. A new endovascular approach to restore valve competency in the superficial and deep venous systems (VNUS vein treatment system). *J Endovasc.Surg* 1999;**6**:98-9.

9. Manfrini S, Gasbarro V, Danielsson G, Norgren L, Chandler JG, Lennox AF *et al*. Endovenous management of saphenous vein reflux. Endovenous Reflux Management Study Group. *Journal of Vascular Surgery.* 2000;**32**:330-42.

10. Merchant RF, DePalma RG, Kabnick LS. Endovascular obliteration of saphenous reflux: a multicenter study.[see comment]. *Journal of Vascular Surgery.* 2002;**35**:1190-6.

11. Mulkens PJM. New results of endovenous radiofrequency therapy (VNUS) of varicose veins: A three year follow-up. *Vasomed* 2003;**. 15**.

12. Pichot O, Kabnick LS, Creton D, Merchant RF, Schuller-Petroviae S, Chandler JG. Duplex ultrasound scan findings two years after great saphenous vein radiofrequency endovenous obliteration. *Journal of Vascular Surgery.* 2004;**39**:189-95.

13. Pichot O, Sessa C, Chandler JG, Nuta M, Perrin M. Role of duplex imaging in endovenous obliteration for primary venous insufficiency. *J Endovasc.Ther* 2000;**7**:451-9.

14. Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H *et al*. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. *J Vasc.Surg* 2002;**35**:958-65.

15. Rautio TT, Perala JM, Wiik HT, Juvonen TS, Haukipuro KA. Endovenous obliteration with radiofrequency-resistive heating for greater saphenous vein insufficiency: a feasibility study. *J Vasc.Interv.Radiol* 2002;**13**:569-75.

16. Rosenblatt, M. Treatment of venous Insufficiency due to greater saphenous vein reflux with endovenous radiofrequency ablation. A conference abstract from the Society of International Radiology 2003. http://directory.sirweb.org/eseries/amabst/display.cfm?ID=99

17. Sybrandy JE,.Wittens CH. Initial experiences in endovenous treatment of saphenous vein reflux. *J Vasc.Surg* 2002;**36**:1207-12.

18. Weiss RA,.Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radiofrequency catheter under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. *Dermatol Surg* 2002;**28**:38-42.

19. Whiteley M, Holdstock JM, Price BA, Scott MJ, Gallagher TM. Radiofrequency ablation of refluxing great saphenous system, Giacomini veins and incompetent perforation veins using VNUS closure and TRLOT technique. *Phlebology* 2003;**18**:52.

Appendix 4 The excluded studies of effectiveness

1. Bergan JJ, Kumins NH, Owens EL, Sparks SR. Surgical and endovascular treatment of lower extremity venous insufficiency. [Review] [42 refs]. J Vasc.Interv.Radiol 2002;13:563-8.
   This is a review article
2. Bhattacharya V. VNUS closure. Whiteley M. VNUS closure - Reply. *Phlebology* 2003;**18**:103-4.
   A letter, no data
3. Bone C,.Navarro L. Endovenous laser: A new minimally invasive technique for the treatment of varicose veins. Endolaser. *Anales de Cirugia Cardiaca y Cirugia Vascular* 2001;**7**.
   Not RFA
4. Chandler JG, Pichot O, Sessa C, Schuller-Petrovic S, Osse FJ, Bergan JJ. Defining the role of extended saphenofemoral junction ligation: a prospective comparative study. *J Vasc.Surg* 2000;**32**:941-53.
   A suspected duplicate study
5. Fassiadis N, Kianifard B, Holdstock JM, Whiteley MS. A novel endoluminal technique for varicose vein management: The VNUS closure. *Phlebology* 2002; **16**:145-8. A descriptive article of RFA
6. Fassiadis N, Kianifard B, Holdstock JM, Whiteley MS. No recurrence of reflux following endovascular radiofrequency ablation of the long saphenous vein (VNUS Closure) at one year. *British Journal of Surgery* 2001;**88**:49-50.
   A duplicate
7. Fischell TA, Haddad N, Baskerville S, Foster MT. Ultrasound thrombolysis for the treatment of thrombotic occlusion of degenerated saphenous vein grafts. *Catheterization & Cardiovascular Interventions* 2000;**. 50**.
   Not for varicose veins
8. Goldman MP. Closure of the greater saphenous vein with endoluminal radiofrequency thermal heating of the vein wall in combination with ambulatory phlebectomy: preliminary 6-month follow-up.[see comment]. *Dermatol Surg* 2000;**26**:452-6.
   This is a duplicate study of an included one
9. Guptan RC. Regarding "Is there an increased risk for DVT with VNUS closure procedure?".[comment]. *J Vasc.Surg* 2003;**38**:1140.
   This is a letter, no data provided
10. Harris EJ. Radiofrequency ablation of the long saphenous vein without high ligation versus high ligation and stripping for primary varicose veins: pros and cons. [Review] [14 refs]. *SEMIN* 2002;**15**:34-8.
    A review
11. Kalra M, Gloviczki P, Noel AA, Rooke TW, Lewis BD, Jenkins GD *et al*. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency--is it justified? *Vasc.Endovascular Surg* 2002;**36**:41-50.
    This is not RFA
12. Komenaka IK,.Nguyen ET. Is there an increased risk for DVT with the VNUS closure procedure? *J Vasc.Surg* 2002;**36**:1311.
    A letter, no data
13. McEvoy FJ, Webbon PM, Gaffney PJ. An experimental clot model in sheep; generation of a heterologous clot and its detection in vivo using venography and labelled fibrinogen. *Research in Veterinary Science* 2002;**. 72**.
    An animal study

14. Merchant R, Jr., Kistner RL, Kabnick LS. Is there an increased risk for DVT with the VNUS closure procedure?[comment]. *Journal of Vascular Surgery.* 2003;**38**:628.
A letter, no data

15. Merchant RF, Kistner RL, Kabnick LS. Regarding "Is there an increased risk for DVT with the VNUS closure procedure?". *J Vasc.Surg* 2003;**38**:628.
A letter, no data

16. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long-term results. *J Vasc.Interv.Radiol* 2003;**14**:991-6.
This is not a RFA

17. Pichot O, Sessa C, Bosson JL. Duplex imaging analysis of the long saphenous vein reflux: basis for strategy of endovenous obliteration treatment. *Int Angiol* 2002;**21**:333-6.
There is no RFA intervention

18. Proebstle TM. Comment on R. A. Weiss : "comparison of endovenous radiofrequency versus 810 nm diode laser occlusion of large veins in an animal model". *Dermatol Surg* 2002;**28**:648.

This is an animal study

19. Sato DT, Goff CD, Gregory RT, Walter BF, Gayle RG, Parent FN, III et al. Subfascial perforator vein ablation: comparison of open versus endoscopic techniques. *J Endovasc.Surg* 1999;**6**:147-54.
Not RFA

20. Sillesen HH, Lundgren J, Sr., Jorgensen M, Bing MH, Baekgaard N, Jensen LP. Local thrombolysis in deep venous thrombosis (DVT) of the lower extremity. *Ugeskrift for Laeger* 2002;.**164**:28.
Not for varicose veins

21. Weiss RA. Comparison of endovenous radiofrequency versus 810 nm diode laser occlusion of large veins in an animal model.[see comment]. *Dermatol Surg* 2002;**28**:56-61.
This is an animal study

22. Wittens CHA, Van Dijk LC, Du Bois NAJJ, Van Urk H . A new 'closed' in situ vein bypass technique. *European Journal of Vascular Surgery* 1994; **8**.
Not for varicose veins

Appendix 5 The excluded studies of the economic evaluation

The following references are excluded because they are not related to the use radiofrequency ablation in the treatment of varicose veins.

1. Early discharge after operations for hernia or varicose veins. *Lancet* 1979;**2**:186.
2. [Differential therapy of chronic wounds]. [German]. *Hautarzt* 1997;**48**:1-4.
3. Adler MW, Waller JJ, Creese A, Thorne SC. Randomised controlled trial of early discharge for inguinal hernia and varicose veins. *J Epidemiol Community Health* 1978;**32**:136-42.
4. Allaert FA, Levardon M, Vin F. [The effect of obesity on venous disease. A study of concomitant factors]. [French]. *Phlebologie* 1991;**44**:271-8.
5. Archampong EQ,.Darko R. Day surgery at Korle Bu Teaching Hospital: a six year review. *West Afr.J Med* 1996;**15**:143-8.
6. Arom KV, Emery RW, Flavin TF, Petersen RJ. Cost-effectiveness of minimally invasive coronary artery bypass surgery. *Ann Thorac.Surg* 1999;**68**:1562-6.
7. Augustin M, Dieterle W, Zschocke I, Brill C, Trefzer D, Peschen M *et al* . Development and validation of a disease-specific questionnaire on the quality of life of patients with chronic venous insufficiency. *Vasa* 1997;**26**:291-301.
8. Avila PC. Prevention of atherosclerosis in coronary-artery bypass grafts.[comment]. *N Engl J Med* 1997;**336**:1839-40.
9. Baker DM, Turnbull NB, Pearson JC, Makin GS. How successful is varicose vein surgery? A patient outcome study following varicose vein surgery using the SF-36 Health Assessment Questionnaire. *Eur J Vasc.Endovasc.Surg* 1995;**9**:299-304.
10. Balzer K. [Ambulatory surgery in venous surgery]. [German]. *Chirurg* 1991;**62**:598-603.
11. Balzer K. [What is the difference between ambulatory care and inpatient varicose vein patients?]. [German]. *Kongressbd.Dtsch.Ges.Chir Kongr.* 2001;**118**:486-91.
12. Belcaro G, Cesarone MR, Nicolaides AN, De Sanctis MT, Incandela L, Geroulakos G. Treatment of venous ulcers with pentoxifylline: a 6-month randomized, double-blind, placebo controlled trial. *Angiology* 2002;**53 Suppl 1**:S45-S47.
13. Bello YM,.Falabella AF. The role of graftskin (Apligraf) in difficult-to-heal venous leg ulcers. *J Wound Care* 2002;**11**:182-3.
14. Bennett G. Using compression hosiery to combat venous leg ulcers. [Review] [17 refs]. *Community Nurse* 1955;**6**:49-52.
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Appendix 6 Based on Jadad's score for Quality assessment of Rautio et al

A. **Randomisation**	**Y**	**N**	**?**
1. Was the RCT described as randomised?	Y		
2. Was allocation truly random? Randomisation described			?

B. **Concealment** of allocation

Was concealment of treatment allocation truly adequate? Stated method	Y		

C. **Masking**

1. Was the trial described as double blind?		N	
2. Was treatment allocation masked from participants?			?
3. Was treatment allocation masked from investigators?			?
4. Was treatment allocation masked from outcome assessors?			?

D. **Completeness** of trial

1.Were the number of withdrawals in each group stated?	Y		
2. Was an intention to treat analysis done?		N	
3.Were the drop out rates similar in both groups?	Y		

Score

Add if A1 YES	+1
Add if C1 YES	+1
Add if D1 YES	+1
Add if A2 YES	+1
Subtract if A1 is YES and A2 is NO or B is NO	-1
if C2 is YES and C4 is YES	+1
Subtract if C1 is YES and C2 is NO or C4 is NO	-1
Total score (between 0 and 5)	2

Others:

1. Validity of the outcome measures discussed? No
2. Were the power and sample size calculations performed? No

Y (Yes), N (No),? (Can't tell)

Appendix 7 Based on Jadad's score for Quality assessment of Lurie et al

A. **Randomisation**	**Y**	**N**	**?**
1. Was the RCT described as randomised?	Y		
2. Was allocation truly random? Randomisation described			?

B. **Concealment** of allocation

Was concealment of treatment allocation truly adequate? Stated method			?

C. **Masking**

1. Was the trial described as double blind?		N#	
2. Was treatment allocation masked from participants?			?
3. Was treatment allocation masked from investigators?			?
4. Was treatment allocation masked from outcome assessors?			?

D. **Completeness** of trial

1.Were the number of withdrawals in each group stated?	Y		
2. Was an intention to treat analysis done?		N	
3.Were the drop out rates similar in both groups?		N	

Score

Add if A1 YES	+1
Add if C1 YES	+1
Add if D1 YES	+1
Add if A2 YES	+1
Subtract if A1 is YES and A2 is NO or B is NO	-1
if C2 is YES and C4 is YES	+1
Subtract if C1 is YES and C2 is NO or C4 is NO	-1
Total score (between 0 and 5)	1

Others:

1. Validity of the outcome measures discussed? No
2. Were the power and sample size calculations performed? No

Y (Yes), N (No),? (Can't tell)

Appendix 8 Study characteristics of radio frequency ablation studies

Author/ Year/Country	*Design*	Number= (Intervention) Age & Sex (% Female)	Number= (Control) Age & Sex (% Female)	Inclusion criteria	Exclusion criteria	Intervention	Follow up	Comments
1.Rautio *et al* 2002 Finland and Canada Ref 28	*RCT*	RFA n=15 Mean age 33 years 93% F	Stripping n=13 Mean age 38 years 92% F	Consecutive patients scheduled for surgery for primary uncomplicated GSV tributary varicose veins	Bilateral, larger GSV diameter (12mm) or tortuous GSV, , if not suitable for day-case surgery	RFA	50 days for both arms	85/121 consecutive patients scheduled were excluded. Previous intervention or associated conditions were not reported. This study seems to exclude all difficult cases.
2. Lurie *et al* 2003 Multicentres Ref 29	*RCT*	n=45 patients but 46 limbs RFA Mean age 49 years 74% F	n=40 patients S&L Mean age 47 72% F	Symptomatic VV confirmed by duplex ultrasound scanning, age: 21-80 years, CEAP C2-C4, ambulatory status, Saphenous vein diameter is less than 1.2 CM in supine position.	Subjectively assessed on the bases of appearance and ultrasound.	RFA	At 72 hours, 1 week, 3 weeks and 4 months.	Previous interventions for VV are considered among the exclusion criteria. No significant differences at base line.
3. Whiteley *et al* 2003 UK ref 30	*Case series*	750 legs in 490 patients	No control	Patients with venous reflux even with cardiac pacemakers.	Technically unsuitable veins, thrombophlebitis, and short saphenous reflux	RFA	First week postoperatively and up to 3 years	This abstract gives little details of the patients' characteristics. i.e. age sex associated conditions
4. Rosenblatt 2003 USA Abstract only ref 31	*Case series*	139 limbs of 124 patients	No control	Symptomatic GSV insufficiency	Not stated	RFA	Up to two years	Lack of important details
5. Dauplaise and Weiss 2001 Multicentres in USA ref 32	*Case series*	288 patients (316 legs) 76% F	No Control	Non-aneurysmal saphenous vein reflux in veins less than 12 mm in diameter	Overly tortuous veins	RFA	Up to 6 months	Associated conditions: 21% of limbs have high ligation, 61% of limbs had phlebectomy concomitantly. Age not stated.
6. Goldman and Amiry 2002 USA ref 33	*Case series*	50 patients 54 legs Mean age 47 years 76% Females	No control	Sequential patients presenting to clinic with in competent greater saphenous vein	Not stated	RFA plus phlebectomy	Up to 24 month	There is no information to indicate the cases are primary of have previously had any interventions. Disagreements between numbers stated in tables and in text for initial patient number and denominator for complications.
7. Merchant et al 2002 USA ref 34	*Case series*	268 patients (318 legs) Mean age 47 years 74% Females	No control	Patients with reflux in non-aneurysmal veins less than 12 mm in lumen diameter measured with duplex scanning in supine position	Limbs with tortuous veins were excluded	RFA and Phlebectomy in 59% and sclerotherapy in 4%	Up to 24 months	The majority of limbs are in classification CEAP 2 (70%). High ligation of saphenofemoral junction was not done.

Author/ Year/Country	*Design*	Number= (Intervention) Age & Sex (% Female)	Number= (Control) Age & Sex (% Female)	Inclusion criteria	Exclusion criteria	Intervention	Follow up	Comments
8. Weiss and Weiss 2002 USA ref 35	*Case series*	120 patients 140 legs 82/120 (63%) Females	No control	Patients with large painful varicosities from the SFJ to about the knee level	Not stated	RFA	Up to 24 months	Age of participants was not stated
9. Fassiadis *et al* 2002 ref 36	*Case series*	79 patients 127 legs Mean 42 years [22-92] 61/79 (77%) Females	No control	Patients with primary varicose veins, recurrence or concomitant ulceration	Not stated	RFA	Up to 12 months	Patients treated between March 1999 and October 2000. 28 legs had recurrent varicose veins and 4 had concomitant ulcer
10. Sybrandy and Wittens 2002 Netherlands ref 37	*Case series*	26 patients 26 legs Mean age 47 18/26 (69%) females	No control	Patients with incompetence of LSV with a diameter of up to 12 mm	Not stated	RFA	Up to 1 year	No additional surgical procedures performed VNUS Medical Technologies support has not been clearly stated apart from the acknowledgment
11.Fassiadis *et al* 2002 UK ref 38	*Case series*	12 patients 18 legs Mean age 51 years 12/12 Females (100%)	No control	Patients with varicose veins who had undergone previous high tie and stripping procedures	Not stated	RFA	Up to 12 months	All patients had general anaesthetic Three legs were treated with additional subfascial endoscopic perforator surgery
12. Rautio *et al* 2002 Finland Feasibility study ref 39	*Case series*	27 patients, 30 legs 24 women and 3 men	No control	Symptomatic mild to moderate varicose veins and primary GSV insufficiency diagnosed with colour duplex US	Heavily tortuous or large >12 mm in diameter greater saphenous trunks	RFA	Up to 1 year	It is not clear if this study is a duplicate to the one of ref 13, same authors, year and number of patients
13. Pichot *et al* 2000 USA ref 40	*Case series*	17 patients, 18 legs Mean age 48 years Range [29-74] 12/17 Females (71%)	No control	Patients presenting with varicose GSV	Not stated	RFA	Up to 6 months	The aim of the study was to assess the role of duplex imaging in defining suitable pathological anatomy for RFA
14. Mulkens 2003 Germany Conference abstract German language ref 41	*Case series*	Number of veins treated 244	No control	Not stated	Not stated	RFA	Up to 3 years	Lack of details in this abstract, and the unit of assessment is veins rather than limbs or patients
15. Fassiadis *et al* 2003 UK ref 42	*Case series*	40 patients, 59 legs Mean age 45 Range age [22-92] 35/40 Females (88%)	No control	Patients with proven venous incompetence (duplex examination) regardless of concomitant ulceration or previous varicose veins	Straight LSV with no aneurismal, tortuous or thrombosed sections	RFA	Up to 1 year	Only 1/59 was lost to follow up
16. Manfrini etal *1999 Italy* Abstract only, Ref 43	*Case series*	10 patients Age [8-50] 8/10 (80%) Females	No control	Patients with saphenofemoral reflux	Not stated	RFA	6 months	Lack of details for patients characteristics

Author/ Year/Country	*Design*	Number= (Intervention) Age & Sex (% Female)	Number= (Control) Age & Sex (% Female)	Inclusion criteria	Exclusion criteria	Intervention	Follow up	Comments
17. Pichot *et al* 2004 Multicentres Ref 44	*Case series*	56 patients, 63 limbs Median age 50 range [27-74] 41/56 Females (73%)	No control	Symptomatic varicose veins with GSV incompetence	Not stated	RFA with adjunctive stab-avulsion phlebotomies	Up to a median follow up 25 months	Three authors declared being paid as consultants to VNUS Medical Technology, two hold shares of the company's restricted stock.
18. Manfrini *et al* 2000 Multicentres Ref 45	*Non randomised comparative study*	142 patients	68 patients treated with Restore	Patients with demonstrable saphenous vein reflux	Not stated	RFA	Up to 1 year	Three authors are consultants paid by VNUS Medical Technology, have shares of the company's stock The proportion of gender is not stated in each treatment group, age was given as mean age 45 for the total patients of which 154/210 (73%) Females
19. Chandler et al 2000 Multicentres Ref 46	*Case series*	301 limbs, 273 patients Mean age 47 y 206/271 Females (76%)	No control	Patients with varicose veins who were 21-80 y and had symptomatic demonstrable saphenous vein reflux	Patients with excluded if they are on anticoagulation or with concomitant peripheral arterial disease	RFA and high ligation, RFA and stab avulsion phlebotomies	Mean follow up 4.9 months	Treated patients had Mean CEAP Clinical Class of 2.4 60% treated with RAF plus phlebotomy, 22 % RAF plus high ligation. The remaining 18% is not stated

Appendix 9 Quality and threats to validity in the included studies of radio frequency ablation

Author / Year / Country	Were cases followed prospectively?	Were cases describe as consecutive? For non (RCT)	Was anything done to reduce bias selection?	Were baseline characteristics provided?	Could there be systematic differences between RFA and control groups if any?	How representative the study is	Length of follow up & What (%) of pts were followed to the final assessment?	Details of the Validity of measurements	If an RCT Concealment Randomisation ITT Blinding Or potential biases
1. Rautio *et al* 2002 Finland and Canada Ref 28	Yes, for a short term only (50 days)	RCT	Randomisation	Yes for mean age Gender BMI Mean maximum diameter of GSV Occupation CEAP classification	The mean age was 5 years younger for the RFA.	Because of exclusion of complicated cases, the result may apply to non severe cases only. External validity is compromised as 121 patients screened but 33 patients randomised.	50 days. 83% in RFA 76% in control	The Validity RAND-36 Duplex, ultrasonography CEAP scoring, VCSS, VSDS, VDS, VAS, were not stated.	- Concealment was by a sealed envelope - No details how randomisation was carried out. - Loss to follow up was 1/16 RFA v 4/17 control. - No blind assessment. - Not ITT
2. Lurie *et al* 2003 Multicentres Ref 29	Yes	RCT	Randomisation	Yes for age, Varicose clinical severity score Gender CEAP clinical classification	No significant differences stated	Complicated cases were excluded i.e. vein diameter >1.2 cm of tortuosity of GSV	Up to 4 months	Validity of: - CIVIQ2 QoL - Clinical examination - Ultrasound were not stated	- No details about concealment or randomisation - loss to follow up 3/44 limbs in RFA v 5/36 control -No blinding - no ITT.
3. Whiteley *et al 2003 UK* Ref 30	Not clear	Not stated	No details	Not stated	No control	The study will not be suitable for patients with the exclusion criteria	Up to three years % Followed to the last assessment 9/750 (1.2%) assessed at three years	Validity of ultrasonography was not stated	Serious losses to follow up bias as only 9/750 were followed up to 3 years.
4. Rosenblatt 2003 USA Abstract only Ref 31	Not stated	Not stated	Not stated	Not stated	Not stated	Lack of details	Up to two years but % of those last assessed can not be calculated	Validity of ultrasound was not stated	Mean follow up was 3.4 months.
5. Dauplaise and Weiss 2001 Multicentres in USA Ref 32	Not stated	Not stated	Not stated	Yes for symptoms of: leg pain, leg fatigue, oedema and varicose veins	No control	Does not apply if met any of the listed exclusion criteria. The majority of cases were females 76%	6 months, however 29% assessed at 6 months	Not stated	Loss to follow up not stated. Possible unit of analysis error, legs not patients analysed. Conflict of interest is not declared: One of the authors is a consultant at the VNUS

Author/ Year/ Country	Were cases followed prospectively?	Were cases describes as consecutive? For non (RCT)	Was anything done to reduce bias selection?	Were baseline characteristics provided?	Could there be systematic differences between RFA and control groups if any?	How representative the study is	Length of follow up & What (%) of pts were followed to the final assessment?	Details of the Validity of measurements	If an RCT Concealment Randomisation ITT Blinding Or potential biases
6. Goldman and Amiry 2002 USA Ref 33	Not clear	Not stated	Consecutive patients presenting to clinic with in competent greater saphenous vein	Yes	No control	Details about symptoms related, occupation, weight could be of value when considering external validity.	6 months, 9 patients were lost to follow up after 6 months i.e. 9/50 (18%) legs lost to follow up.	Duplex ultrasound validity is not stated	Unit of analysis (patient or leg) is not clear, patient satisfaction implies if the recommended people would have similar severity that patients have. The statement that the authors have indicated no significant interest with commercial supporters needs to be explained.
7. Merchant et al 2002 USA Ref 34	Yes	Not stated	Not stated	Yes for symptoms and for mean symptom severity scores.	No control	Further details about occupation, and weight could be of value when considering external validity.	Only 142/318 (45%) legs were assessed at 24 months	Duplex ultrasound, CEAP classifications, patient satisfaction to recommend the procedure and symptom severity score, all these are not validated.	Adjunctive procedures used. This would make it difficult to attribute the effectiveness specifically to RFA. Some cases had general anaesthesia. The lead author has been paid by VNUS a consulting fee for providing educational opportunity for staff. Stating the outcomes of those who were available for assessment rather than out of those who had the intervention carried out analysis.
8. Weiss and Weiss 2002 USA Ref 35	Not clear	Not clear	Not stated	Yes for associated symptoms	No control	Data about age was not reported	At 24 months: 21/140 (15%) were followed at 24 years	Not stated	All equipment used were paid for from VNUS company. Analysis was done by evaluating the available cases for assessment and not in relation to patients started the trial. Therefore the loss to follow up is a major bias.
9. Fassiadis *et al* 2002 Ref 36	Not stated	Not stated	Not stated	Not stated	No control	The range of age was [22-92] 28 legs had	12 months, 28 /127 legs excluded, therefore	Not stated	The study considered available patients only in terms of recurrence of the reflex. The loss to follow up

						recurrent varicose veins, 4 with ulcers	78% considered for last assessment		up to 78% is a major bias.
10. Sybrandy and Wittens 2002 Netherlands Ref 37	Retrospectively	Not stated	Not stated		No control		12 months, 26/26 followed to 1 year	Not stated	
11.Fassiadis *et al* 2002 UK Ref 38	Not stated	Not stated	Not stated		No control		12 months, 10/12 (83%) of patients assessed at 12 months	Not stated	
12. Rautio *et al* 2002 Finland Ref 39	Not stated	Not stated	Not stated		No control		12 months, 19/27 (70%) followed up to 1 year	Not stated	
13. Pichot *et al* 2000 USA Ref 40	Not stated	Not stated	Not stated		No control		Up to 6 months, 18/18 assesses	Not stated	
14. Mulkens 2003 Germany Conference abstract Ref 41	Not stated	Not stated	Not stated		No control		Up to 3 years, 68/244 (28%) of veins assessed at three years relative to those assessed at 6 weeks	Not stated	
15. Fassiadis *et al* 2003 UK Ref 42	Not stated	Not stated	Not stated		No control		12 months, 1/58 (1.7%) assessed at 12 months	Not stated	
16. Manfrini etal 1999 Italy Abstract Ref 43	Not stated	Not stated	Not stated		No control		6 months, 10/10 (100% assessed at 6 months.	Not stated	
17. Pichot *et al* 2004 Multicentres Ref 44	Not stated	Not stated	Not stated		No control		Up to 24 weeks, 63/63 limbs assessed at 3 years	Not stated	
18. Manfrini *et al* 2000 Multicentresef 45	Not stated	Not stated	Not stated		Control: Restore procedure		Up to one year, 19/68 (28%) assesses at 1 year	Not stated	
19. Chandler et al 2000 Multicentres Ref 46	Not stated	Not stated	Not stated		No control		Up to one year, 19/301 (6.3%) assessed at one year	Not stated	

Appendix 10 Effectiveness data

Author/ Year/ Country	Population	Intervention	Comparator (if any)	Measures of outcomes	Results/Changes relative to baseline Size of effect & Adverse effects	Duration of follow up	Comments
1.Rautio *et al* 2002 Finland and Canada Ref 28	Patients scheduled for surgical treatment who met the inclusion criteria.	RFA	Conventional stripping surgery	(a) Colour duplex scan. (b) Postoperative venous segmental disease score. (c) Decrease in venous clinical severity (d) Decrease in venous disability score (e) visual analogue scale (f) Complications (g) RAND-36 (h) Sick leave	- Operating time: 75 min RFA v 57 min stripping p=0.003 - Post op VSDS fell from 1 to 0 in RFA in 15/15 (100%) patients v 1/13 (8%). - Decrease in VCSS: 5.1 (SD 1.5) stripping 4.4 (SD 1.1) p=0.19 - Post-operative VDS: VNUS score 0 in 14/15 (93%) v Stripping score 0 in 12/13 (92%) - Pain VAS: significant differences in favour of VNUS in terms of Rest, Standing and walking. - Use of analgesia: (Average daily number of 600 mg ibuprofen tablets) VNUS 0.4 (SD 0.49) v stripping 1.3 (SD 1.06) p=0.004 - Intra op complications: RFA 3/15 (20%) second degree thermal v stripping 1/13 groin haematoma. - QoL (RAND-36): only bodily pain was significant in favour of VNUS. - Sick leave: VNUS 6.5 (SD 3.3) v Stripping 15.6 (SD 6.0) p,0.001 - Satisfaction: RFA 1/15 (7%) dissatisfied with cosmetic outcome v stripping 4/13 (31%). - Cost: RFA direct cost is higher; if indirect cost is taken into account then VNUS is more cost effective. - Post op complications: saphenous nerve parasthesia RFA 2/15 (13%) v stripping 3/13 (23%), clinical thrombophlebitis VNUS 3/15 v stripping 0, local haematoma RFA 1/15 (7%) v stripping 4/13 (31%), thermal skin injury RFA 1/15 (7%) stripping 4/13 (31%), Total events: VNUS 7/15 (49%), stripping 7/13 (54%).	50 days for both arms	Only short term recovery and cost were compared Longer term follow up for recurrence was not the aim of the study. Small sample size study. Mean age in the RFA is five years younger.
2. Lurie *et al* 2003 Multicentres Ref 29	Patients with symptomatic varicose veins and GSV incompetence confirmed with ultrasound scanning. Age 21-80 years and CEAP C2 to C4.	RFA	Ligation & stripping surgery	- CIVIQ2 QoL - Clinical examination - Ultrasound	- Time to return to normal work was statistically significant 4.7 days in RFA v 12.4 S&L - QoL survey (global score, pain, physical) at 72h and at 1 week showed statistical differences in favour of the RFA, however, the difference progressively decreased between 1 week and 4 months. - Complications were statically significant (in favour of RFA) at 72 h, 1 week and 3 weeks for tenderness, ecchymosis and haematoma. - in no cases did flow reappear after complete occlusion of the GSV	At 72 hours, 1 week, 3 weeks, and 4 months	VNUS Medical Technologies provided financial support.
3. Whiteley et al 2003 UK Ref 30	Patients with venous reflux	RFA	No control	Scanning	Success of closure by scanning in 130/131 assessed at 1 year, 42/42 in the 2 nd year and 9/9 at the 3 rd year.	Up to 3 years	Serious loss to follow up cases as 130/750 assessed in the first year, 42/750 in the second year and 9/750 were assessed at the third year. I have contacted the author for further details but he did not provide any.

<table>
<tr><th>Author/ Year/ Country</th><th>Population</th><th>Intervention</th><th>Comparator (if any)</th><th>Measures of outcomes</th><th>Results/Changes relative to baseline
Size of effect &
Adverse effects</th><th>Duration of follow up</th><th>Comments</th></tr>
<tr><td>4. Rosenblatt 2003 USA
Abstract only
Ref 31</td><td>Symptomatic greater saphenous vein reflux</td><td>RFA</td><td>No control</td><td>Symptom relief
Sonographic occlusion
Complications
Recanalisation</td><td>Symptom relief: 135/139 (97%) symptomatic improvement but not stated at what time.
Sonographic occlusion: recanalisation in 6/139 (4%)
Complications: mild transient Paresthesia 16/139 (11%), 2/139 (1.4%) skin burns.
No DVT
4/139 (3%) partial occlusion was seen.
6/139 (4.3%) recanalisation of GSV</td><td>Up to two years</td><td>Serious lack of details in this abstract presented at the Society of Interventional Radiology meeting in the US.</td></tr>
<tr><td>5. Dauplaise and Weiss 2001
Multicentres in USA
Ref 32</td><td>Patients with not overly tortuous varicose veins less than 12 mm in diameter</td><td>RFA</td><td>No control-Before and after analysis</td><td>Pain, fatigue, oedema, absence of reflux, adverse events, patient satisfaction</td><td>Symptoms resolution (the unit is leg):<table><tr><td>Symptom</td><td>Pre treatment n=316</td><td>6 weeks n=228</td><td>6 months n=93</td></tr><tr><td>Leg pain</td><td>251 (79%)</td><td>44 (19.3%)</td><td>8 (8.6%)</td></tr><tr><td>Leg fatigue</td><td>216 (68%)</td><td>24 (10.5%)</td><td>3 (3.2%)</td></tr><tr><td>oedema</td><td>105 (33%)</td><td>19 (8.3%)</td><td>2 (2.2%)</td></tr><tr><td>Varicose veins</td><td>3.8 (97%)</td><td>14 (6.1%)</td><td>5 (5.4%)</td></tr></table>Adverse events:<table><tr><td></td><td>Within 1 week</td><td>6 months</td></tr><tr><td>DVT</td><td>3/288 (1%)</td><td>0/93</td></tr><tr><td>Skin burns</td><td>8/288 (2.8%)</td><td>0/93</td></tr><tr><td>Clinical phlebitis</td><td>9/288 (3.1%)</td><td>2/93 (2.2%)</td></tr><tr><td>Paresthesia above calf treatment</td><td>31/288 (13.6%)</td><td>3/53 (5.7%)</td></tr></table>Patient satisfaction: at 6 months 83/88 (94%) patients would recommend the procedure.</td><td>6 months</td><td>Only the % of those assessed at a particular time stated i.e. Loss to follow up is not stated.</td></tr>
<tr><td>6. Goldman and Amiry 2002 USA
Ref 33</td><td>Sequential patients presenting to clinic with in competent greater saphenous vein</td><td>RFA plus phlebectomy</td><td>No control</td><td>Procedure time, resumption of activity, duplex evaluation of reflux, adverse events and patients satisfaction</td><td>- Time to do the procedure is on average: 7 minutes. Average catheter pullback rate was 2.76 cm/min, average length of treated GSV was 19 cm.
-95% can resume preoperative activities within 24 hours.
- Complete elimination of pain and fatigue
- 100% would recommend RFA to a friend
- Post-op duplex evaluation (legs):<table><tr><td>Vein closed</td><td>68%</td></tr><tr><td>Vein open without reflux</td><td>22%</td></tr><tr><td>Vein open with reflux</td><td>10%</td></tr><tr><td>Recurrent veins</td><td>7%</td></tr><tr><td>Recurrent symptoms</td><td>2%</td></tr></table>Adverse events:
- 20/50 legs (56%) purpura
- Erythema 5/50 (10%)
Fibrous cord 5/80 legs (16%) over the site of ambulatory phlebectomy.</td><td>Up to 24 months</td><td>It is not clear if the claimed effectiveness is due to RFA, ambulatory phlebectomy or both.</td></tr>
</table>

<table>
<tr><th>Author/ Year/ Country</th><th>Population</th><th>Intervention</th><th>Comparator (if any)</th><th>Measures of outcomes</th><th>Results/Changes relative to baseline
Size of effect &
Adverse effects</th><th>Duration of follow up</th><th>Comments</th></tr>
<tr>
<td>7. Merchant et al 2002 USA
Ref 34</td>
<td>Patients met the inclusion criteria listed in table 1</td>
<td>RFA and Adjunctive procedures (phlebectomy, sclerotherapy) see comments</td>
<td>No control, analysis done before and after the interventions</td>
<td>Occlusion measured by duplex scanning, clinical symptoms scores, physical evaluation and patient satisfaction and reported adverse events.</td>
<td>Occlusion status:
At 24 months: Complete occlusion i.e. veins with no evidence of flow 121/142 (85.2%), recanalisation 16/142 (11.3%)
Mean symptom severity score:
At 24 months: for pre-treatment 2:00 v complete occlusion with no evidence of flow 0.10, recanalisation 0.63.
Physician assessment of the outcome (by limb) at 24 months:
CO: 98% successful
Recanalisation: 38% successful.
Symptoms status at 24 months:
<table><tr><th></th><th>pain</th><th>fatigue</th><th>oedema</th><th>pigments</th><th>Dermal sclerosis</th></tr><tr><td>Pre</td><td>83%</td><td>76%</td><td>30%</td><td>22%</td><td>7%</td></tr><tr><td>CO</td><td>3%</td><td>2%</td><td>4%</td><td>7%</td><td>0.8%</td></tr><tr><td>ReCan</td><td>25%</td><td>19%</td><td>13%</td><td>19%</td><td>13%</td></tr></table>(Pre:pre-treatment, CO: complete occlusion, ReCan: recanalisation >5 cm of flow in the treated vein segment)
Adverse events:
- DVT 3/286 legs (1%) of which 1 had pulmonary embolism
Skin burn:
6/143 (4.2%)
- Clinical phlebitis:
6/286 (2%)
- Paresthesia:
43/286 (15%)
Patient satisfaction at 24 months:
CO: 96% would recommend
Recanalisation: 80%</td>
<td>Up to 24 months</td>
<td>General anaesthesia used at some centres but most used local (tumescent or regional or both) with or without sedation.
Adjunctive procedures phlebectomy in 187 limbs (59%), sclerotherapy in 11 limbs (4%).

The mean symptom severity scores reduced from 2.00 at pre-treatment to 0.63 post treatment at 24 weeks with recanalisation. Could that be a placebo effect?</td>
</tr>
<tr>
<td>8. Weiss and Weiss 2002 Multicentres USA

Ref 35</td>
<td>Patients with incompetent SFJ</td>
<td>RFA</td>
<td>No control</td>
<td>Procedure time
Absence of duplex determined by ultrasound flow.
Symptom resolution and patient satisfaction</td>
<td>Time procedure: average time from access to completion is 52 min.
Vein occlusion: at 24 months 19/21 (90%) had complete disappearance of the treated saphenous vein.
Symptoms: (unit is leg)
<table><tr><th>symptoms</th><th>Pre n=140</th><th>6 weeks n=102</th><th>2 years n=21</th></tr><tr><td>Leg pain</td><td>119 (85%)</td><td>5(5%)</td><td>1(5%)</td></tr><tr><td>Leg fatigue</td><td>119 (85%)</td><td>7 (7%)</td><td>1(5%)</td></tr><tr><td>oedema</td><td>27 (19%)</td><td>2(2%)</td><td>0(0%)</td></tr></table>Satisfaction: 98% patients would recommend RFA at 6 months.
Adverse events: at 6 months: only 1/102 (1%) Paresthesia reported.</td>
<td>Up to 24 months</td>
<td>Phlebectomy performed concomitantly in 87/147 (62% legs) this makes it difficult to attribute effectiveness to RFA.</td>
</tr>
</table>

Author/ Year/ Country	Population	Intervention	Comparator (if any)	Measures of outcomes	Results/Changes relative to baseline Size of effect & Adverse effects	Duration of follow up	Comments
9.a. Fassiadis *et al* 2002 UK Ref 36	Patients with varicose veins regardless of recurrence or concomitant ulceration	RFA	No control	- Reflux by duplex ultrasound following the RFA - Mobility following RFA - Recurrence	- all patients were fully mobile within 12 h - 80, 51, 42, 28 patients were available at 6 weeks, 3 months, 6 months and 12 months respectively. - one leg had a reflux in the lateral thigh branch	From immediately after RFA, 6 weeks, 3 months, 6 months and 12 months	There is a lack of important details
10. Sybrandy and Wittens 2002 Netherlands. Ref 37	Patients with incompetence of LSV with a diameter of up to 12 mm	RFA	No control	-Reflux by Duplex ultrasound scan - Complications - CEAP Score	CEAP score was significantly improved postoperatively The overall complication rate was 23% Technical failure 1 (3.8%) Recanalization 1 (3.8%) Partial Recanalization with SFJ incompetence 1 (3.8%) Total Recanalization and failure 3 (11.5%) Closure of JSV and SFJ 13 (50%) LSV closure with competence of SFJ 2 (7.7%) LSV closure with SFJ incompetence 8 (30.8%) Total closure of LSV 23 (88.5%)		Varicose veins with tortuocity were not excluded and this would explain the higher rate of complication. It was stated that all the complications happened in the first half of the studied population, indicating a learning curve effect.
11.b Fassiadis *et al* 2002 Ref 38	Patients with varicose veins who had undergone previous high tie and stripping procedures	RFA	No control	Recanalisation proven by duplex ultrasound scan Days needed to return to work Mean duration of RFA surgery Complications	LSVs remained closed throughout the surveillance period in all assessed patients. 3 days to return to work Mean time of the VNUS surgery 17 minutes Sensory disturbances noted in 6 legs, however they were only temporary	Up to 12 months	Patients have had previous stripping 2/12 lost to follow up
12. Rautio *et al* 2002 Finland Feasibility study Ref 39	Symptomatic mild to moderate varicose veins and primary GSV insufficiency diagnosed with colour duplex US	RAF	No control	- Obliteration of the GSV demonstrated by duplex - Recurrence of new varicosities - Complications	- 22/30 (73%) successfully treated legs - Treatment failure of 11/30 (36%) events (more than one event in a treated leg is possible) of which 8/30 (27%) recurrence of reflux and 3/30 (10%) recurrence of varicosities - Complications: vein perforation 2/30 (7%), saphenous nerve paresthesia 3/30 (10), clinical thrombophlebitis 2/30 (7%), 1/30 (3%) skin injury.	Up to one year	Details Midterm follow up were stated, although only 21 legs of 19 patients were followed-up.
13. Pichot *et al* 2000 USA Ref 40	Patients presenting with varicose GSV	RAF	No control	- Anatomical changes following RFA in the saphenofemoral junction	At 1 week, the saphenous trunks of all 10 limbs were either shrunken and obliterated n-7 or occluded by a thrombus without shrinkage n=11 At 6 months 7 GSVs were no longer sonographically visible, 10 were shrunken and obliterated 1 had a segmental partial Recanalization. By 6 months 1 limb had total SFJ occlusion, the other 14 had at least 1 persistent or reopened tributary	Up to 6 months	This study reported only the anatomical changes to the saphenofemoral junction and the saphenous trunk incompetence

Author/ Year/ Country	Population	Intervention	Comparator (if any)	Measures of outcomes	Results/Changes relative to baseline Size of effect & Adverse effects	Duration of follow up	Comments
14. Mulkens 2003 Germany Conference abstract German language Ref 41	Varicose veins of GSV	RFA	No control	- Reflux free veins - Recurrence of new veins - Satisfaction - Adverse events	- 60 veins assessed at 3 years, reflux free was 68% - No evidence of neovascularisation at 3 year assessment by duplex sonography - satisfaction was 95% with the procedure but no details if it is symptom related - Adverse events were: PE I case (0.3%), leg venous thrombosis 3 cases (0.9%), thrombophlebitis (3.70%) number of cases or the denominator were not stated, paresthesia 14% after 1 week 55 after 2 years (number of cases or the denominator were not stated, skin burns 7 cases (2%) at the beginning of the study.	Last assessment carried forward was up to 3 years	The unit of analysis was the number of veins rather than a treated leg Lack of essential details regarding the number of case reported and the denominator
15. Fassiadis *et al* 2003 UK Ref 42	Patients with proven venous incompetence (duplex examination) regardless of concomitant ulceration or previous varicose veins	RFA	No control	- Closure of LSV demonstrated by duplex - Mobility following the procedure - Return to normal daily activity - Treatment failure - Adverse events	Postoperative LSV closure on duplex reported in the immediate, 6 weeks, 3 months, 6 months, 9 months and 12 months follow up showed: 58 (100%), 31(100%), 17(100%), 6(100%) and 1(100%) respectively.	Immediately and up to 1 year following the procedure	A huge loss to follow up rate at 1 year over 99%, yet the author followed only one patient at one year and reported as 100% closure on duplex.
16. Manfrini etal 1999 Italy Abstract only Ref 43	Patients with saphenofemoral reflux	RFA	No control	Recurrence of reflux following the RFA	9/10 patients, reflux was completely eradicated at 6 months follow up	6 months follow up	There is a lack of essential details in this abstract
17. Pichot *et al* 2004 Multicentres Ref 44	Symptomatic varicose veins with GSV incompetence	RFA with adjunctive stab-avulsion phlebotomies	No control	- Duplex finding following RFA - Neovascularity - Symptom score improvement	- GSV truncal occlusion was observed in 57/63 limbs 90.5% of treated GSVs at 2 years. - Varicosities following RAF & adjunctive phlebotomy 7.9% - Symptom score improvement in 95% of limbs	Up to 2 years follow up	With adjunctive therapy, it would be inappropriate to attribute the success to the new intervention.
18. Manfrini *et al* 2000 Multicentres Ref 45	Patients with demonstrable saphenous vein reflux	RFA, high ligation in 60/151(40%) limbs Phlebectomy in 112/151(74%)	Patients treated with Restore procedure	- Reflux status -Recanalization - Adverse events - Symptoms	- RAF 141/151 (93%) limbs caused acute obliteration, Restore treatment 41/68 (60%) limbs - Early recanalization in RFA in 6%, -Comparing RFA and Restore, there were no statistically significant differences in terms of failure and complications.	Up to one year	Comparative details at baseline for the two procedures are not stated There were adjunctive treatments prior or concurrent to RFA. Data for statistical analysis have been taken from the graphs as data were was not provided in text

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td><table>
<tr><td></td><td colspan="2">RFA and adjunctive n=53</td><td colspan="2">Restore n=31</td></tr>
<tr><td></td><td>Pain</td><td>Varicose veins</td><td>Pain</td><td>Varicose veins</td></tr>
<tr><td>Pre treatment</td><td>72% NS</td><td>96% NS</td><td>76%</td><td>96%</td></tr>
<tr><td>6 weeks</td><td>30% SS</td><td>10% SS</td><td>8%</td><td>36%</td></tr>
<tr><td>6 months</td><td>10% NS</td><td>9% SS</td><td>14%</td><td>52%</td></tr>
<tr><td>12 months</td><td>6% SS</td><td>6% SS</td><td>36%</td><td>40%</td></tr>
</table></td><td></td><td></td></tr>
<tr><td>The 19. Chandler et al 2000
Multicentres
Ref 46</td><td>Patients with varicose veins who were 21-80 y and had symptomatic demonstrable saphenous vein reflux</td><td>RFA and high ligation in 67 limbs (22%), RFA and stab avulsion phlebotomies in (60%)</td><td>No control</td><td>- Being a symptomatic -substantial improvements,
- Complications.</td><td colspan="3">Outcomes at 6 months out of 91 patients assessed:
-76/91 (83.5%) asymptomatic.
-10/91 (11%) substantially improved
-3/91 (3%) unchanged
-2/91 (2%) mild worsening
-Clinical thrombophlebitis 20/300 (6.7%)
-Paresthesia 58/300 (19%)
- Skin injury 8/300 (2.7%)
-Thrombus propagation 3/223 (1.4%) denominator without ligation involving above the knee GSV</td><td>Up to one year
Mean follow up 4.9 months</td><td>Complications were not stated according to what type of adjunctive procedures patients had.
Only 19/273 (7%) patients were assessed at 1 year</td></tr>
</table>

7. References

[1] Campbell B. New treatments for varicose veins. *BMJ* 2002;**324**:689-90.

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