Ontario Health Technology Assessment Series 2011; Vol. 11, No.1

Endovascular Radiofrequency Ablation for Varicose Veins

An Evidence-Based Analysis

February 2011

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Endovascular radiofrequency ablation for varicose veins: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2011 February [cited YYYY MM DD]; 2011; 11(1) 1-94. Available from:
http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas/tech_rfa_vv_20110216.html

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ISSN 1915-7398 (Online)
ISBN 978-1-4435-3506-9 (PDF)

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List of Abbreviations

AVVSS	Aberdeen varicose vein symptom score
CEAP	Clinical, etiological, anatomic, pathological classification
CIV	Chronic venous insufficiency
CIVIQ	Chronic venous insufficiency questionnaire
CCT	Controlled clinical trial
DUS	Duplex ultrasound
DVI	Deep venous insufficiency
DVT	Deep venous thrombosis
ELT	Endovascular laser therapy
EVLA	Endovascular laser ablation
GSV	Great saphenous vein
LEED	Linear endovascular energy density
MAS	Medical Advisory Secretariat
OHTAC	Ontario Health Technology Advisory Committee
OR	Odds ratio
PE	Pulmonary embolism
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
RR	Relative risk
SD	Standard deviation
SFJ	Saphenofemoral junction
SF-36	Medical outcomes study short form
SPJ	Saphenopopliteal junction
SSV	Small saphenous vein
UGFS	Ultrasound guided foam sclerotherapy
VCSS	Venous clinical severity score

Executive Summary

Objective

The objective of the MAS evidence review was to conduct a systematic review of the available evidence on the safety, effectiveness, durability and cost–effectiveness of endovascular radiofrequency ablation (RFA) for the treatment of primary symptomatic varicose veins.

Background

The Ontario Health Technology Advisory Committee (OHTAC) met on August 26th, 2010 to review the safety, effectiveness, durability, and cost-effectiveness of RFA for the treatment of primary symptomatic varicose veins based on an evidence-based review by the Medical Advisory Secretariat (MAS).

Clinical Condition

Varicose veins (VV) are tortuous, twisted, or elongated veins. This can be due to existing (inherited) valve dysfunction or decreased vein elasticity (primary venous reflux) or valve damage from prior thrombotic events (secondary venous reflux). The end result is pooling of blood in the veins, increased venous pressure and subsequent vein enlargement. As a result of high venous pressure, branch vessels balloon out leading to varicosities (varicose veins).

Symptoms typically affect the lower extremities and include (but are not limited to): aching, swelling, throbbing, night cramps, restless legs, leg fatigue, itching and burning. Left untreated, venous reflux tends to be progressive, often leading to chronic venous insufficiency (CVI). A number of complications are associated with untreated venous reflux: including superficial thrombophlebitis as well as variceal rupture and haemorrhage. CVI often results in chronic skin changes referred to as stasis dermatitis. Stasis dermatitis is comprised of a spectrum of cutaneous abnormalities including edema, hyperpigmentation, eczema, lipodermatosclerosis and stasis ulceration. Ulceration represents the disease end point for severe CVI. CVI is associated with a reduced quality of life particularly in relation to pain, physical function and mobility. In severe cases, VV with ulcers, QOL has been rated to be as bad or worse as other chronic diseases such as back pain and arthritis.

Lower limb VV is a very common disease affecting adults – estimated to be the 7th most common reason for physician referral in the US. There is a very strong familial predisposition to VV. The risk in offspring is 90% if both parents affected, 20% when neither affected and 45% (25% boys, 62% girls) if one parent affected. The prevalence of VV worldwide ranges from 5% to 15% among men and 3% to 29% among women varying by the age, gender and ethnicity of the study population, survey methods and disease definition and measurement. The annual incidence of VV estimated from the Framingham Study was reported to be 2.6% among women and 1.9% among men and did not vary within the age range (40-89 years) studied.

Approximately 1% of the adult population has a stasis ulcer of venous origin at any one time with 4% at risk. The majority of leg ulcer patients are elderly with simple superficial vein reflux. Stasis ulcers are often lengthy medical problems and can last for several years and, despite effective compression therapy and multilayer bandaging are associated with high recurrence rates. Recent trials involving surgical treatment of superficial vein reflux have resulted in healing and significantly reduced recurrence rates.

Endovascular Radiofrequency Ablation for Varicose Veins

RFA is an image-guided minimally invasive treatment alternative to surgical stripping of superficial venous reflux. RFA does not require an operating room or general anaesthesia and has been performed in an outpatient setting by a variety of medical specialties including surgeons and interventional radiologists. Rather than surgically removing the vein, RFA works by destroying or ablating the refluxing vein segment using thermal energy delivered through a radiofrequency catheter.

Prior to performing RFA, color-flow Doppler ultrasonography is used to confirm and map all areas of venous reflux to devise a safe and effective treatment plan. The RFA procedure involves the introduction of a guide wire into the target vein under ultrasound guidance followed by the insertion of an introducer sheath through which the RFA catheter is advanced. Once satisfactory positioning has been confirmed with ultrasound, a tumescent anaesthetic solution is injected into the soft tissue surrounding the target vein along its entire length. This serves to anaesthetize the vein, insulate the heat from damaging adjacent structures, including nerves and skin and compresses the vein increasing optimal contact of the vessel wall with the electrodes or expanded prongs of the RF device. The RF generator is then activated and the catheter is slowly pulled along the length of the vein. At the end of the procedure, hemostasis is then achieved by applying pressure to the vein entry point.

Adequate and proper compression stockings and bandages are applied after the procedure to reduce the risk of venous thromboembolism and to reduce postoperative bruising and tenderness. Patients are encouraged to walk immediately after the procedure. Follow-up protocols vary, with most patients returning 1 to 3 weeks later for an initial follow-up visit. At this point, the initial clinical result is assessed and occlusion of the treated vessels is confirmed with ultrasound. Patients often have a second follow-up visit 1 to 3 months following RFA at which time clinical evaluation and ultrasound are repeated. If required, additional procedures such as phlebectomy or sclerotherapy may be performed during the RFA procedure or at any follow-up visits.

Regulatory Status

The Closure System® radiofrequency generator for endovascular thermal ablation of varicose veins was approved by Health Canada as a class 3 device in March 2005, registered under medical device license 67865. The RFA intravascular catheter was approved by Health Canada in November 2007 for the ClosureFast catheter, registered under medical device license 16574. The Closure System® also has regulatory approvals in Australia, Europe (CE Mark) and the United States (FDA clearance). In Ontario, RFA is not an insured service and is currently being introduced in private clinics.

Methods

Literature Search

The MAS evidence–based review was performed to support public financing decisions. The literature search was performed on March 9th, 2010 using standard bibliographic databases for studies published up until March, 2010.

Inclusion Criteria

- English language full-reports and human studies
- Original reports with defined study methodology
- Reports including standardized measurements on outcome events such as technical success, safety,

effectiveness, durability, quality of life or patient satisfaction

- Reports involving RFA for varicose veins (great or small saphenous veins)
- Randomized controlled trials (RCTs), systematic reviews and meta-analyses
- Cohort and controlled clinical studies involving ≥ 1 month ultrasound imaging follow-up

Exclusion Criteria

- Non systematic reviews, letters, comments and editorials
- Reports not involving outcome events such as safety, effectiveness, durability, or patient satisfaction following an intervention with RFA
- Reports not involving interventions with RFA for varicose veins
- Pilot studies or studies with small samples (< 50 subjects)

Summary of Findings

The MAS evidence search on the safety and effectiveness of endovascular RFA ablation of VV identified the following evidence: three HTAs, nine systematic reviews, eight randomized controlled trials (five comparing RFA to surgery and three comparing RFA to ELT), five controlled clinical trials and fourteen cohort case series (four were multicenter registry studies).

The majority (12/14) of the cohort studies (3,664) evaluating RFA for VV involved treatment with first generation RFA catheters and the great saphenous vein (GSV) was the target vessel in all studies. Major adverse events were uncommonly reported and the overall pooled major adverse event rate extracted from the cohort studies was 2.9% (105/3,664). Imaging defined treatment effectiveness of vein closure rates were variable ranging from 68% to 96% at post-operative follow-up. Vein ablation rate at 6-month follow-up was reported in four studies with rates close to 90%. Only one study reported vein closure rates at 2 years but only for a minority of the eligible cases. The two studies reporting on RFA ablation with the more efficient second generation catheters involved better follow-up and reported higher ablation rates close to 100% at 6-month follow-up with no major adverse events. A large prospective registry trial that recruited over 1,000 patients at thirty-four largely European centers reported on treatment success in six overlapping reports on selected patient subgroups at various follow-up points up to 5 year. However, the follow-up for eligible recruited patients at all time points was low resulting in inadequate estimates of longer term treatment efficacy.

The overall level of evidence of randomized trials comparing RFA with surgical ligation and vein stripping (n = 5) was graded as low to moderate. In all trials RFA ablation was performed with first generation catheters in the setting of the operating theatre under general anaesthesia, usually without tumescent anaesthesia. Procedure times were significantly longer after RFA than surgery. Recovery after treatment was significantly quicker after RFA both with return to usual activity and return to work with on average a one week less of work loss. Major adverse events occurring after surgery were higher [(1.8% (n=4) vs. 0.4% (n = 1) than after RFA but not significantly. Treatment effectiveness measured by imaging defined vein absence or vein closure was comparable in the two treatment groups. Significant improvements in vein symptoms and quality of life over baseline were reported for both treatment groups. Improvements in these outcomes were significantly greater in the RFA group than the surgery group in the peri-operative period but not in later follow-up. Follow-up in these trials was inadequate to evaluate longer term recurrence for either treatment. Patient satisfaction was reported to be high for both treatments but was higher for RFA.

The studies comparing endovascular treatment approaches for VV (RFA and ELT) were more limited. Three RCT studies compared RFA (two with the second generation catheter) with ELT but mainly focused on peri-procedural outcomes such as pain, complications and recovery. Vein ablation rates were not evaluated in the trials, except for one small trial involving bilateral VV. Pain responses in patients undergoing ablation were extremely variable and up to 2 weeks, mean pain levels were significantly less with RFA than ELT ablation but differences were not significant at one month. Recovery, evaluated as return to usual activity or return to work, however, was similar in the treatment groups. Vein symptom and QOL improvements were improved in both groups but were significantly better in the RFA group than the ELT group at 2 weeks, but not at one month. Vein ablation rates were evaluated in several controlled clinical studies comparing the treatments between centers or within centers between individuals or over time. Comparisons in these studies were inconsistent with vein ablation rates for RFA reported to be similar to, higher than and lower than those with ELT.

Economic Analysis

RFA and surgical vein stripping, the main comparator reimbursed by the public system, are comparable in clinical benefits. Hence a cost-analysis was conducted to identify the differences in resources and costs between both procedures and a budgetary impact analysis (BIA) was conducted to project costs over a 5-year period in the province of Ontario. The target population of this economic analysis was patients with symptomatic varicose veins and the primary analytic perspective was that of the Ministry of Health and Long-Term Care.

The average case cost (based on Ontario hospital costs and medical resources) for surgical vein stripping was estimated to be $1,799. In order to calculate a procedural cost for RFA it was assumed that the hospital cost and physician labour fees, excluding anaesthesia and surgical assistance, were the same as vein stripping surgery. The manufacturer also provided details on the generator with a capital cost of $27,500 and a lifespan of 5 years and the disposables (catheter, sheath, guidewire) with a cost of $673 per case. The average case cost for RFA was therefore estimated to be $1,356. One-way sensitivity analysis was also conducted with hospital cost of RFA varied to 60% that of vein stripping surgery (average cost per case = $627.08) to calculate an impact to the province.

Historical volumes of vein stripping surgeries in Ontario were used to project surgeries in a linear fashion up to five years into the future. Volumes for RFA and ELT were calculated based on share capture from the surgery market based on discussion with clinical expert opinion and existing private data based on discussion with the manufacturer. RFA is expected to compete with ELT and capture some of the market. If ELT is reimbursed by the public sector then numbers will continue to increase from previous private data and share capture from the conventional surgical treatment market. Therefore, RFA cases will also increase since it will be capturing a share of the ELT market. A budget impact to the province was then calculated by multiplying volumes by the cost of the procedure.

RFA is comparable in clinical benefits to vein stripping surgery. It has the extra upfront cost of the generator and cost per case for disposables but does not require an operating theater, anaesthetist or surgical assistant fees. The impact to the province is expected to be 5 M by Year 5 with the introduction of new ELT and RFA image guided endovascular technologies and existing surgery for varicose veins.

Conclusion

The conclusions on the comparative outcomes between endovascular RFA and surgical ligation and saphenous vein stripping and between endovascular RFA and laser ablation for VV treatment are summarized in the table below (ES Table 1).

ES Table 1: Outcome comparisons of RFA vs. surgery and RFA vs ELT for varicose veins

Outcome Comparisons	RFA vs Surgery	RFA vs ELT
Post procedural pain, minor complications	RFA < Surgery	RFA < ELT
Recovery	RFA < Surgery	RFA ~ ELT
Major adverse events	RFA < Surgery	RFA ~ ELT
Effectiveness - Imaging vein occlusion/ absence	RFA ~ Surgery	RFA ? ELT
Effectiveness -Vein symptom improvement	RFA ~ Surgery	RFA ~ ELT
Effectiveness - Quality Of Life	RFA ~ Surgery	RFA ~ ELT
Recurrence	RFA ? Surgery	RFA ? ELT
Patient satisfaction	RFA > Surgery	RFA ? ELT
Patient preference	RFA > Surgery	RFA ? ELT
Procedure costs	RFA < Surgery	RFA ~ ELT
Budget impact	RFA < Surgery	RFA ~ ELT

ELT refers to endovascular laser ablation; RFA, radiofrequency ablation

The outcomes of the evidence-based review on these treatments for VV based on different perspectives are summarized below:

RFA First versus Second Generation Catheters and Segmental Ablation

- Ablation with second generation catheters and segmental ablation offered technical advantages with improved ease and significant decreases in procedure time. RFA ablation with second generation catheters is also no longer restricted to smaller (< 12 mm diameter) saphenous veins.

- The safety profile with the new device and method of energy delivery is as good as or improved over the first generation device. No major adverse events were reported in two multicenter prospective cohort studies in 6 month follow-up with over 500 patients. Post-operative complications such as bruising and pain were significantly less with RFA ablation with second generation catheters than ELT in two RCT trials.

- RFA treatment with second generation catheters has ablation rates that are higher than with first generation catheters and are more comparable with the consistently high rates of ELT.

Endovascular RFA versus Surgery

- RFA has a quicker recovery attributable to decreased pain and lower minor complications.
- RFA, in the short term was comparable to surgery in treatment effectiveness as assessed by imaging defined anatomic outcomes such as vein closure, flow or reflux. Other treatment outcomes such as symptomatic relief and HRQOL were significantly improved in both groups and between group differences in the early peri-operative period were likely influenced by pain experiences.
- Longer term follow-up was inadequate to evaluate recurrence after either treatment.
- Patient satisfaction was high after both treatments but was higher for RFA than surgery.

Endovascular RFA versus ELT

- RFA has significantly less post-operative pain than ELT but differences were not significant when

pain was adjusted for analgesic use and pain differences between groups did not persist at 1 month follow-up.

- Treatment effectiveness, measured as symptom relief and QOL improvement were similar between the endovascular treatments in the short term (within 1 month)
- Treatment effectiveness measured as imaging defined vein ablation was not measured in any RCT trials *(only for bilateral VV disease)* and results were inconsistently reported in observational trials.
- Longer term follow-up was not available to assess recurrence after either treatment.

System Outcomes – RFA *Replacing Surgery or Competing with ELT*

- RFA may offer system advantages in that the treatment can be offered by several medical specialties in outpatient settings and because it does not require an operating theatre or general anaesthesia.
- The treatment may result in decanting of patients from OR with decreased pre-surgical investigations, demand on anaesthetists' time, hospital stay and wait time for VV treatment. It may also provide more reliable outpatient scheduling.
- Procedure costs may be less for endovascular approaches than surgery but the budget impact may be greater with insurance of RFA because of the transfer of cases from the private market to the public payer system.
- Competition between RFA and ELT endovascular approaches is likely to continue to stimulate innovation and technical changes to advance patient care and result in competitive pricing.

Background

Objective of Analysis

The objective of this MAS report was to conduct a systematic review of the available evidence on the safety, effectiveness, durability and cost–effectiveness of endovascular radiofrequency ablation (RFA) for the treatment of primary symptomatic varicose veins (VV).

Clinical Condition

Varicose veins are tortuous, twisted, or elongated veins. (1) The primary cause of the condition is poorly functioning valves and decreased elasticity in the vein walls, resulting in venous reflux (reversed blood flow in the vein); it may also be the result of prior thrombotic events. (2) The resultant blood pooling leads to an enlargement of the veins with smaller vessels developing telangiectasis (spider veins) and larger vessels such as the saphenous veins becoming elongated and tortuous. The symptoms of patients with VV can include: aching leg pain, leg swelling, throbbing, night cramps, restless legs, leg fatigue and heaviness, and/or itching and burning.(3;4) Untreated venous reflux has also been associated with various complications such as varices rupture with hemorrhage and superficial thrombophlebitis. (1) It may also lead to chronic venous insufficiency (CVI) with prevalence increasing with age. (5) CVI itself is a pathological condition of the skin and subcutaneous tissues that is secondary to prolonged stasis of venous blood flow. (6) The clinical signs of CVI result from venous hypertension occurring over time causing chronic inflammation, which further leads to a spectrum of conditions including edema, hyperpigmentation, eczema, lipodermatosclerosis and ulcers. (7) Leg ulcers represent the disease end-point for severe CVI.

Prevalence and Incidence

Varices of the lower limbs is a very common adult disease and estimated to be the seventh most common reason for referral to a physician in the US. (8) A familial predisposition to VV is likely as the risk in offspring is 90% if both parents are affected, 45% (25% boys, 62% girls) if only one parent is affected, and 20% when neither affected. (9) The prevalence of VV worldwide ranges from 5% to 15% among men and 3% to 29% among women. (5) The variability in this prevalence is attributable to a range of factors and a function of the age of the population studied, gender distribution (higher in women), ethnicity of the study group (more common in Caucasians than Blacks or Asians), survey methods, and disease definition. The annual incidence of VV estimated from the Framingham Study was reported to be 2.6% among women and 1.9% among men and did not vary within the age range (40 to 89 years) studied. (10)

Leg ulcers of venous origin are also common in the adult population. Approximately 1% of the adult population has a leg ulcer of venous origin at any one time and 4% are at of risk of leg ulcer. (11) The majority of leg ulcer patients are elderly and have simple superficial venous reflux. Episodes of leg ulcers are lengthy, lasting in some cases for several years. In a UK population based study, the median duration of ulceration was nine months, while 20% of the ulcers had not healed within two years and 66% of the patients had episodes of ulceration lasting longer than five years. (8) Management of leg ulcers is also difficult. Although initial compression and multilayer bandaging have been shown to be effective, the recurrence is high. (12;13) Recent trials involving superficial vein surgery for treatment of vein reflux have resulted in initial healing and significantly reduced recurrence with leg ulcers. (14;15)

Disease Measurement

The internationally accepted classification system for chronic venous disease, the clinical status, etiology,

anatomy and pathophysiology (CEAP) system was first developed in 1994 by a multidisciplinary committee convened by American Venous Forum. (16) The system recently underwent a revision and has been approved as part of the reporting standards for endovenous ablation treatment of venous insufficiency by the American Venous Forum and the Society of Interventional Radiology. (17;18) The nomenclature of the lower limb venous system has also recently been revised by an international interdisciplinary panel to standardize and improve diagnosis, care and research into venous disorders. (19;20) The veins are divided into three systems: the superficial, deep and perforating. The superficial veins, consisting of the saphenous veins, their tributaries and accessory and communicating vessels, are located in the subcutaneous tissue and are the major causes of varicose veins. The saphenous veins include the great saphenous vein (GSV) and the small saphenous veins (SSV). The junctions where these veins meet with the deep venous system are called the saphenofemoral junction (SFJ) and the saphenopopliteal junction (SPJ), which are also critical areas for occurrence of reflux.

Duplex ultrasonography is the recommended optimal approach for investigating diseases and disorders of the venous system. (21;22) It provides a map to document the extent of venous disease and presence of reflux in the superficial venous system and the deep venous systems. (20) This is essential to differentiate the relative involvement of the deep and superficial venous systems and the junctions and connectors between them in order to guide the selection of the appropriate treatment. Duplex ultrasound also has a role in surveillance after therapy to assess outcomes and detect recurrence.

A potential classification system for saphenous vein reflux was developed following a duplex ultrasound imaging survey of 2,275 limbs in 1,751 patients. The 5-point category system was based on the combination of varices, saphenous vein reflux, junction reflux, or malleus reflux that were present. (23)The most common source of saphenous insufficiency was the GSV in 82.7% (n=1,882) of cases and less commonly the SSV (10.9%; n=248) and non saphenous veins (6.4%; n=145). Varices without reflux, estimated to occur in 36.7% of cases, were thought to involve consultations mainly for aesthetic purposes. The overall proportion of limbs that were asymptomatic was 34.4%. Reflux affecting the entire saphenous system from the saphenous junction down to the ankle was reported to more likely affect the oldest patients ($\geq$ 63 years).

Vein Symptoms and HRQOL

A number of measures exist to evaluate symptoms and severity of vascular disease. The Venous Clinical Severity Scale (VCSS) has been a recommended instrument to report symptom severity. (17;18;24) It's based on physician assessment of nine common symptoms: pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, ulcers (number, state, size) of chronic venous disease, and the use of compression therapy. (24;25)

The impact of varicose veins on health related quality of life (HRQOL) has also been evaluated in several clinical (26-28) and population (29) based surveys. Quality of life (QOL) was measured by SF-36 (a generic QOL instrument) and several disease-specific QOL instruments including the VEINES-QOL/Sym, CIVIQ-2, and the Aberdeen QOL. In general, chronic venous disease was found to be associated with significantly reduced HRQOL, particularly in relation to pain, physical function and mobility. There was also a strong linear trend of increasing impact on physical functioning and disability with respect to activities of daily living with increasing disease severity. In an international survey of patients presenting to general practitioners and vein disease specialists, 65% of patients with VV had additional disease processes such as oedema, skin changes or ulceration. (28) Physical and mental HRQOL scores were reported to decrease with the severity of symptoms and in the most severe cases, HRQOL rated by the SF-36 was worse than that of patients with chronic lung disease, back pain, or arthritis. VV alone without symptoms, however, was not found to alter HRQOL.

Management Varicose Veins

Varicose veins are initially managed with conservative therapy involving life style changes such as weight loss through diet and regular exercise, as well as elevation of the feet at the end of the day. (1) Compression therapies including the use of prescribed elastic or support stockings are also frequently recommended to decrease blood volume, oedema, venous distension, and venous wall tension. (7) These therapies are also used to increase calf muscle pump function, which is one of the major sources of venous return. This can improve venous hemodynamics in patients with VV and reduce oedema, but poor compliance attributable to the cost of the stockings, lack of patient education, and poor cosmesis, limits their effectiveness. Various pharmacological treatments and herbal supplements have also been used to treat symptoms, including diuretics for oedema, topical steroid creams for dermatitis, and antibiotics for infection involving stasis ulcers. (7)

Sclerotherapy, is a major first therapy for smaller veins like telangiectasias or spider veins and is one of the most common venous procedures performed in an office setting. (30;31) The technique involves the injection of a chemical irritant into the veins which subsequently initiates a chemical thrombophlebitis, occlusion and subsequent vein fibrosis. Many different chemical materials are used as sclerosing agents. (31) Sclerosing foam has been increasing used because of advantages over liquid sclerosants in displacing blood rather than being diluted by blood, having an increased contact with endothelium and being echogenic greatly increasing treatment accuracy. (32) The major considerations for sclerotherapy have been about maximizing treatment efficacy while minimizing risk by using the proper sclerosant for the vein to be treated. (2;31) Risks to treatment efficacy occur with too low a dose and increased risk of complications such as DVT or emboli can occur with too high a dose. (33) Sclerotherapy, however, remains the treatment of choice for smaller diameter (< 4 mm) leg veins with less severe disease and without vein reflux are often treated effectively although multiple repeat sessions are often required. (2;34) In practice because recanalization rates and recurrence rates are common in patients, sclerotherapy is generally reserved for isolated varices without truncal reflux or for residual varices after surgery or intravascular ablation therapies. (34)

Ambulatory phlebectomy (PB) is another common procedure for VV that is usually performed in outpatient settings. (2) In the procedure, phlebectomy hooks are used to remove tributary veins of the saphenous veins through multiple skin incisions. Combination treatments involving PB with surgical or endovascular treatments such as radiofrequency or laser ablation may also be performed. Only local anaesthesia is required and is referred to as tumescent anaesthesia which involves the injection of an anaesthetic solution, usually lidocaine, into the perivenous space along the length of the treated vein. This method eliminates multiple needle sticks and allows rapid anaesthesia to extensive vein segments. It also produces local swelling and tissue firmness, reduces blood loss, decreases bruising, and increases patient comfort.

Surgery has been the mainstay treatment for superficial veins such as the great saphenous vein (GSV) and the small saphenous vein (SSV), which are the major cause of leg varicose veins. (35) The surgery is performed in the operating room under general, spinal, or epidural anaesthesia. The operative technique involves an initial ligation of the saphenofemoral junction (SFJ) followed by a stripping of the GSV. The stripping is usually only performed to the knee because of concerns over increased saphenous vein injury. (36) There is morbidity following surgery including a range of complications such as neurosensory loss, infection, hematomas lymph leaks, or deep vein thrombosis (DVT) reported to occur in approximately 18% to 20% of patients. (37;38) Patients also often require 2 to 3 weeks recovery time after surgery and, despite advances in techniques, high recurrence rates have continued. (39)

Endovascular techniques such as radiofrequency (RFA) or endovascular laser ablation (ELT) are major treatment alternatives to surgery for varicose veins. Both techniques involve ablation or destruction of the vein wall through thermochemical reactions. Most patients with superficial saphenous vein reflux are

generally suitable for endovascular approaches. In a recent UK study, patient suitability for various endovascular treatments and surgery was assessed through duplex ultrasonography. (40) A total of 403 consecutive patients referred to a regional vascular center with five vascular surgeons for open surgery for varicose veins underwent ultrasonographic assessments. Treatment eligibility was based on anatomic considerations including vein diameter, tortuosity and the presence intraluminal thrombus. Patients were then categorized with: GSV diameters 3-12 mm suitable for RFA, diameters > 3 mm suitable for ELT, diameters < 1 cm suitable for foam sclerotherapy. Overall, 328 (73%) of the legs were suitable for at least one of the three endovascular approaches. The major reasons for exclusions included vein tortuosity or thrombosis.

Endovascular Radiofrequency Ablation

RFA is an image guided, minimally invasive treatment alternative to surgery for the treatment of VV reflux. The treatment does not require an operating room or general anaesthesia and has been performed in outpatient settings by various medical specialties including surgeons (vascular or general), and interventional radiologists. It is generally considered after treatment with conservative therapy has failed. Although most patients with VV reflux are eligible for the treatment, their anatomy must be amenable. Veins that are too small or tortuous for catheter access or too large to successfully ablate would not be appropriate. Other contraindications considered to the treatment include: pregnancy, inability to ambulate, poor general health, aneurysmal sources of venous reflux, and a compromised deep venous vascular system.

RFA occludes veins through conductive thermal heating. The first generation catheters had expanding electrodes which delivered bipolar energy directly into the vein wall to coagulate the tissue in the vein. In RFA, the electrodes are typically in contact with portions of the vein wall during heating. Successful ablation of the target vein results from tumescent-induced and heat-induced venous spasm to bring the vein wall maximally into contact with the electrodes which deliver thermal energy resulting in endothelial denudation and collagen shrinkage of the vein.

RFA seems to be more dependent on adequate vein emptying, use of tumescent anaesthesia, and compression techniques than endovascular laser ablation techniques which do not depend on vein wall contac. Tumescent anaesthesia, which is the subcutaneous injection of anaesthetic solution along the target vein, is an essential part of both ablation procedures. In addition to providing anaesthesia, it has a compression effect on the vein (both hydrostatic physical compression and pharma-induced spasm) which maximizes the RFA ablative effects on the vein wall. When delivered in a sufficient volume it also separates the vein from surrounding structures protecting other nerves and skin structures. It also acts as a thermal sink, which reduces peak temperatures in perivenous tissues.

Treatment with RFA begins with a color-flow Doppler ultrasonography exam to confirm and map all areas of venous reflux. (41-43) The procedure then involves the percutaneous introduction of a guide wire into the target vein under ultrasound guidance followed by the insertion of an introducer sheath through which an RFA catheter carrying the radiofrequency energy is advanced to a location near the SFJ. Once satisfactory positioning has been confirmed with ultrasound, a tumescent anaesthetic solution is injected into the soft tissue surrounding the target vein along its entire length. The lower limb is also elevated during treatment to further exsanguinate the vessel.

The electrodes of the catheter are then unsheathed and wall contact and vessel exsanguination are tested through impedance measurement of the catheter. The RFA generator is then activated and after activation of the treatment circuit, the wall temperature is allowed to equilibriate at 85^0 for 15 seconds. Heparinized saline is also administered through the central lumen of the catheter to rinse the electrodes to avoid thrombus formation or blood coagulation. The catheter is then slowly withdrawn at a rate 2-3 cm per second down the vein. To avoid damage to the saphenous nerve the treatment is usually limited to the

area above the medial condyle of the tibia. (44;45) At the end of the procedure, hemostasis is achieved by applying pressure to the entry point.

After the procedure, compression stockings and bandages are applied to reduce postoperative bruising, tenderness, and the risk of venous thromboembolism. (46) Patients are encouraged to walk immediately after the procedure. Follow-up protocols vary, with most patients returning 1 to 3 weeks later for a follow-up visit in which the occlusion of the treated vessels is evaluated with ultrasound. Patients often have a second follow-up visit in the 1 to 3 months following, at which time clinical evaluation and ultrasound are repeated. If required, sclerotherapy may be performed during the RFA procedure or at any follow-up visits.

The second generation of RFA catheters, the ClosureFast was designed to improve on procedural deficiencies such as length of time and ease of the procedure. Unlike the first generation RFA catheter, the ClosurePlus involves a segmental approach to ablation and involves activating the heating element for 20-second cycles. The heat is then automatically shut off and the catheter is repositioned to the next treatment zone indicated by shaft markers on the catheter. The new catheter also no longer needs the saline drip and eliminates the high impedance issues caused by coagulum build up with the previous catheter. The segmental approach, sometimes referred to as segmental RFA ablation (s-RFA) also speeds up the procedure and decreases the variability in dose delivered to the tissue. The new design also involved changes in the method of energy delivery in that the energy field was now shielded and an electrical field is not produced in the tissue thereby reducing the potential concerns for interference with other indwelling devices such as pacemakers etc.

REGULATORY

The Closure System® radiofrequency generator for endovascular thermal ablation of varicose veins was approved by Health Canada as a class 3 device in March 2005, registered under medical device license 67865. The RFA intravascular catheter was approved by Health Canada in November 2007 for the ClosureFast catheter, registered under medical device license 16574. The Closure System® also has regulatory approvals in Australia, Europe (CE Mark) and the United States (FDA clearance). In Ontario, RFA is not an insured service and is currently being introduced in private clinics.

Methods

Research Question(s)

The purpose of this evidence review was to determine the safety, effectiveness and cost-effectiveness of endovascular RFA in the management of primary symptomatic varicose veins. The specific research questions addressed were:

1. What is the broader safety profile of RFA?
2. What is the treatment effectiveness of RFA for varicose vein reflux?
3. What is the treatment effectiveness of RFA for varicose veins symptoms?
4. What is the impact of RFA on health related quality of life?
5. What is the durability of RFA treatment?
6. What is patient satisfaction with RFA treatment?
7. What is the comparative effectiveness of RFA with surgical ligation and vein stripping?
8. What is the comparative effectiveness of RFA with endovascular laser ablation?

Literature Search

A literature search was performed on March 9th, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published up to March, 2010 (Appendix 1). Abstracts (n = 338) were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Additional Information Sources; Consultations with held with clinical experts (vascular surgeons and interventional radiologists) and industry representatives.

Inclusion Criteria

- English language full-reports and human studies
- Original reports with defined study methodology
- Reports including standardized measurements on outcome events such as technical success, safety, effectiveness, durability, quality of life or patient satisfaction
- Reports involving RFA for varicose veins (great or small saphenous veins)
- Randomized controlled trials (RCTs), systematic reviews and meta-analyses
- Cohort and controlled clinical studies involving ≥ 1 month ultrasound imaging follow-up

Exclusion Criteria

- Non-systematic reviews, letters, comments and editorials
- Reports not involving outcome events such as safety, effectiveness, durability, or patient satisfaction following RFA
- Reports not involving interventions with RFA for varicose veins
- Pilot studies or studies with small samples (< 50 subjects)

Outcomes of Interest

The outcomes of interest included: technical outcomes, patient recovery, ultrasound defined absence of flow or absence of vein, vein recanalization, neovascularization, vein reflux, complications, major adverse events, varicose vein symptoms, patient satisfaction and quality of life.

Quality of Evidence

The quality of evidence assigned to individual RCT studies was determined using a modified CONSORT Statement Checklist for Randomized Controlled Trials. (47) The CONSORT Statement was adapted to include three additional quality measures: the adequacy of control group description, significant differential loss to follow-up between groups, and study attrition.

The overall quality of the evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (48) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence Based Analysis

Analysis - Literature Approach

The MAS evidence review was performed to review available evidence on RFA published until March 2010. In particular the literature was reviewed for the following: large studies (> 50) involving effectiveness, complications or adverse events reported in short or longer term cohort follow-up, large cohorts with longer term (> 1-year) follow up, randomization trials or controlled clinical trials comparing RFA with other approaches particularly surgery, which is considered the key comparator for endovascular approaches. The results of this search are outlined in Table 1 and include eight randomized controlled trials, five controlled clinical trials and fourteen cohort case series.

The MAS literature search also identified nine systematic evidence reviews on treatments including endovascular RFA for varicose veins. Three HTA evidence reports on endovascular RFA treatment of VV performed to support public healthcare financing decisions were also identified. (49-51)

The results of the MAS evidence review are detailed below in two sections. The first section involves a summary of the evidence in the systematic reviews. The second section included the evidence from the MAS review that addresses the effectiveness and durability of RFA, safety of RFA and the comparative effectiveness of RFA with surgery (surgical ligation and vein stripping) and the comparative effectiveness of RFA with endovascular laser ablation.

Table 1: Level of Evidence of Included RFA Studies

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT (n> 100), systematic review of RCTs	1	1, 12
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT (n < 100)	2	7
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	5
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	1
Case series (multisite)	4b	2
Case series (single site)	4c	11
Retrospective review, modelling	4d	
Case series presented at international conference	4(g)	

* RCT refers to randomized controlled trial;

Section 1. Published Systematic Evidence Reviews

The summary details of the systematic evidence reviews identified in the literature on RFA of varicose veins are listed below in Table 2. Three HTA evidence reports is support of public funding decisions were performed in two countries, in Australia (50) and in the United Kingdom. (49;51) Nine other systematic evidence reviews on VV treatment were identified, one focused only on RFA (52), one focused on all treatments (53) and the remainder focused on endovascular approaches. (34;39;54-58)

Table 2: Systematic Reviews on Radiofrequency Ablation of Varicose Veins

Author	Report Year	Search Period	Review Objective	Evidence
HTA Evidence Reports				
MAS Ontario, Canada	2010	To March 2010	▪ To review the safety, effectiveness, durability and cost-effectiveness of radiofrequency ablation (RFA) for varicose veins	12 SR, 8 RCT, 5 CCT, 13 case series (>50 patients), 1 multi-center international Registry (6 reports)
Center for Evidence Based Purchasing NHS (51) United Kingdom	2009	1996 - 2008	▪ To assess the value and cost effectiveness of endovascular treatments of varicose veins	5 RCT
ASERNIPS (50) Australia	2008	January 1988 – February 2008	▪ To assess the safety and effectiveness of current treatment options for varicose veins	1 SR, 3 RCT, 1 CCT, 17 case series (Adi et al)
West Midlands HTA Adi et al. (49) United Kingdom	2004	1966 - January 2004	▪ To review the clinical effectiveness and the cost-effectiveness of studies of studies of RFA for the treatment of varicose veins.	2 RCT, (one also a cost study), 17 case series
Systematic Reviews – All Treatments Including RFA for Varicose Veins				
Bacho et al. (54)	2009	Not Stated	▪ To review the evidence regarding studies comparing one intervention against another (compression, sclerotherapy, surgery and endoluminal) for uncomplicated VV	3 RCT RFA versus surgery, 1 RCT RFA versus ELT
Badri et al. (55)	2008	Not stated	▪ To compare the safety and effectiveness of ELT, radiofrequency and sclerotherapy to surgery (ligation and vein stripping) for VV	RFA: 2 RCT, 1 CCT, 4 case series
Beale et al. (34)	2004	Not stated	▪ To compare published evidence on RFA and ELT for VV	RFA; 2 RCT, 15 case series ELT; 7 case series
Gohel et al. (52)	2009	To July 2008	▪ To summarize the evidence for the clinical, quality–of-life outcomes and cost-effectiveness following RFA for superficial venous reflux	3 RCT, 2 meta analyses, 15 prospective observational studies
Leopardi et al. (53)	2009	Jan 1988 – Feb 2008	▪ To review the safety and effectiveness of varicose vein treatments (conservative therapy, sclerotherapy, phlebectomy, ELT, radiofrequency ablation and surgery involving saphenous vein ligation and stripping)	RFA versus surgery (1 SR, 5 RCT, 17 case series)

Author	Report Year	Search Period	Review Objective	Evidence
Luebke et al. (56)	2008	1970 - 2007	▪ To assess the safety/effectiveness of endoluminal therapies (ELT, RF ablation, foam sclerotherapy) compared to conventional surgery	RFA: 5 RCT, 4 CCT, 17 case series
Perrin et al. (39)	2004	Up to June 2004	▪ To analyze published data on RFA and ELT and to compare then with conventional surgery	RFA; 2 RCT RVA vs surgery, 3 trials RFA versus ELT and 30 case series (7 in French)
Subramonia et al. (57)	2007	To 2005	▪ To review the evidence for new endoluminal interventions for lower limb varicoses	RFA: 2 RCT, 5 case series
van den Bos et al. (58)	2009	To Feb 2007	▪ Effectiveness of four therapies for lower extremity varicosities (foam sclerotherapy, ELT, radiofrequency, surgical ligation and stripping)	RFA; 4 RCT, 13 case series

ASERNIPS, refers to the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical; CCT, Controlled clinical trial; CE, Cost effectiveness; CS, Cohort series; ELT, Endovascular laser treatment; HTA, Health technology assessment; MAS, Medical Advisory Secretariat; SR, Systematic review; RFA, Radiofrequency ablation

Section 2. MAS Evidence Review

2A. Effectiveness of Radiofrequency Ablation

Cohort trials evaluating the treatment effectiveness of endovascular RFA involved the Closure System® and two generations of catheter designs - the ClosurePlus the first generation catheter and the ClosureFast the second generation catheter. The details of these studies are summarized in Appendix 2 (Tables A2) and the results on treatment effectiveness are discussed separately below for the two RFA catheter designs.

RFA ClosurePlus Ablation of the Great Saphenous Vein

The majority of the cohort trials (12/14) evaluating safety and effectiveness of RFA for VV involved the first generation catheter, the Catheter Plus and with this, ten cohort studies (n > 50 patients), involving 1,944 patients were identified. All studies were conducted in the United States. The majority of the reports involved single centers but many represented the experience of more than one vascular surgeon. Two international multicenter studies, the Endovenous Reflux Management Study Group (59) and the VNUS Closure Treatment Study Group (60) reported on large numbers of patients undergoing RFA.

The Endovenous Reflux Group study included 210 patients treated at 16 private clinics and university centers in Europe. The VNUS Closure Treatment Study Group was an industry sponsored and maintained prospective registry with 32 sites in Europe, United States and Australia enrolling 1,006 patients (1,222 legs) (61) The registry study had six overlapping reports involving different objectives and varying periods of trial follow-up. (60-65)

Patients and eligibility criteria

The majority of the study participants were women (range 68% - 85%) and the mean age of the patients in these trials, with the exception of two trials (66;67) dealing with specialty groups of VV patients, ranged from 45 to 60 years of age. The Tzillinis et al. (67) study evaluated the operative morbidity in older (≥ 70 years) versus younger (< 70 years) cohorts and the Puggioni et al. (66) trial evaluated the safety of RFA in patients with prior venous thrombotic events.

RFA treatment of symptomatic VV was performed by vascular surgeons in all trials except one (68) where treatment was provided by a dermatologist. RFA procedures were also generally performed in operating room under general anaesthesia. Only four studies (68-71) employed local tumescent anaesthesia with or without conscious sedation.

All of the cohort studies involved the great saphenous vein as the primary target vein. The inclusion criteria for the Catheter Plus trials was also restricted to patients with GSV having vein diameters < 12 mm due to the limitations of the catheter design. There were no cohorts directed to RFA treatment of the small saphenous vein.

Concomitant procedures

Concomitant phlebectomy was performed in the majority (ten studies) of the studies and in four studies SFJ ligation was also performed as adjunct procedures. (59;67;72;73) The need for concomitant SFJ ligation with RFA was assessed in two studies, one involving a within cohort study comparison of RFA performed with and without concomitant SFJ ligation (72) and the other a subset analysis (62) of the VNUS Closure Registry. No concomitant procedures were performed in two trials. (66;70)

Imaging treatment effectiveness

The details of the ten cohort studies and two multicenter international registries reporting on imaging follow up outcomes on RFA ablation of the GSV are outlined below in Tables 3 and 4. Imaging defined anatomic measure of treatment success was generally defined as occlusion of the treated vessel with duplex ultrasound being the imaging modality used in all reports.

Six of these cohort studies reported on imaging defined closure rates at early postoperative follow-up (See Table 3). Ablation in the immediate post-operative period, generally within a month was variably defined as complete closure with no flow or no reflux in the treated vein region and was reported to range from 68% (68) to 98% (71). The VNUS Treatment Study Group, the multicenter international prospective trial, reported a high ablation rate (96.6%) in the first week of follow-up. However, 19.2% (235/1222) of the subjects recruited to the trial had already been lost to follow-up.

Table 3: Post-Operative Imaging Outcomes of RFA ClosurePlus Catheter Ablation of Great Saphenous Vein

Author, Year,	Sample Follow-Up	Treatment Success	Occlusion Rate
Boros, 2008 (72)	142 p (77 p without SFJ ligation) 1 month	Complete ablation as absence of flow in treated vein on duplex ultrasound	92% (71/77)
Dunn, 2006 (69)	68 p (85 L) 3 days	Occlusion of treated vein and absence of reflux on duplex ultrasound	96% (80/83)
Goldman, 2002 (74)	47 p (50 L) 1 month	Occlusion and absence of reflux in treated vein on duplex ultrasound	68% (28/41)
Hingorani, 2004 (75)	66 p (73 L) 1 month	Occlusion of treated vein on duplex ultrasound	96% (70/73)
Weiss, 2002 (71)	120 p (140 L) 1 week	Vein occlusion on duplex ultrasound	98% (137/140)
Welch, 2006 (76)	146 p (184 L) 2-3 months	Vein complete occlusion on duplex ultrasound	77.7% (143/184)
Merchant – Closure Group 2005 (61)	1006 p 1 week	Vein occlusion on duplex ultrasound defined as no evidence of flow from 3 cm below the SFJ along the length of the treated vein and absence of reflux defined as any evidence of reverse flow > 0.5 seconds in any treated vein segment or in the SFJ area (or SPJ)	96.6% (952/985)

Five studies (61;69-71;77) reported on short-term follow-up (around 6 months) on imaging follow-up with the Closure system. Treatment effectiveness was variably defined in the studies as vein occlusion, recanalization or absent reflux. Saphenous vein occlusion rate and absent reflux rate was reported to be a 88% (64/73) in the Dunn et al. (69) trial at 6 months and the overall occlusion rate at 4 months was reported to be 87.1% in the Vasquez et al. (70) trial. Recanalization rates at 6 months were reported to be 15% (15/100) and 3% (3/98) in the Salles-Cunha et al. (77) and the Weiss et al. (71) study respectively. In the Merchant et al. (61) report on the VNUS Treatment Study Group, the vein occlusion rate was reported to be 89.2% at 6 months. At this follow-up point, however, less than half (42%; 518/1220) of the eligible recruited cohort had been reported on. RFA was also reported to significantly improve ulcer healing in the Vasquez et al. study group. The number of limbs with one (5.4% to 0.8%), two (2.2% to 0.3%) or

more than 2 (0.5% to 0) active ulcer sites significantly ($p < .0001$) decreased after RFA.

Longer term follow-up (1-year or beyond) was reported in two trials. (61;71) The Weiss et al. (71) trial reported on 120 recruited patients who were at various stages of 1-year (67 patients) and 2-year (21 patients) follow-up. For the 21 patients seen at 2 years, 19 had complete disappearance of their treated saphenous vein. The longest term follow-up, up to 5 years, has been reported in the VNUS Closure Treatment Study Group. (61) Follow-up in that cohort trial, however, was limited and performed for less than a quarter of the recruited and eligible cohort at all follow-up periods - 23%, (263/1141) at 2 years, 13.4% (133/991) at 3 years, 14.3%, (119/833) at 4 years and 28.8% (117/406) at 5 years. Vein occlusion rates for the various reported subgroups at 2, 3, 4 and 5-year follow-up were reported to be 88.2%, 88.0%, 86.6% and 83.8% respectively. Follow-up occlusion rates for this prospective registry study were also not estimated by life table analysis.

Table 4: Imaging Follow-Up and Outcomes of RFA ClosurePlus Catheter Ablation of Great Saphenous Vein

Author, Year, Country	Sample	Treatment Success	≤3 Months	6 Months
Boros 2008 Michigan, US (72)	219 p (219 Legs) 77 p with RF and SFJ ligation 142 p RF only	▪ Complete ablation as absence of flow in treated vein on duplex ultrasound ▪ Incomplete ablation defined as treated vein having obliterated and patent areas ▪ No ablation patent treated vein	1 month complete ablation RFA + ligation = 92% (71/77) RFA only = 84% (119/142) *p* = .096	-
Dunn 2006 Nevada, US (69)	68 p (85 Legs)	▪ Occlusion of treated vein and absence of reflux on duplex ultrasound at 3 days and 6 months	3 days 96% (80/83) Occluded and absent reflux	88% 64/73) Occluded and absent reflux
Goldman 2002 California, US (68;74)	47 p (50 Legs)	▪ Occlusion and absence of reflux in treated vein on duplex ultrasound at 6, 9 , 12, 18 and 24 months	1 month 68% (28/41) occluded without reflux Recanalization with reflux (n = 4) without reflux (n = 9)	
Hingorani 2004 Florida, US (75)	66 p (73 Legs) 73 GSV	▪ Occlusion of treated vein on duplex ultrasound at 1 month	1 month 96% (70/73)	
Salles-Cunha 2004 Ohio, US (77)	84 p (100 Legs) RF and SFJ ligation in 87% procedures	▪ Occlusion of treated vein on duplex ultrasound and classified as absent (non-visualized), occluded (shrunk, atretic, fibrotic, thrombosed), or recanalized ▪ Average F-Up 8 months (range 4 – 14 months)		Average 8 months Successful ablation 85% (Entire segment absent n=53) or occluded (n = 32), recanalized 15% (15/100)

Author, Year, Country	Sample	Treatment Success	≤3 Months	6 Months
Vasquez 2007 New York, US (70)	499 p (682 Legs) (566 GSV, 95 AASV, 21 SSV)	▪ Vein occlusion on color flow duplex ultrasound at 4 days, 4 weeks, 4 months		4 months Overall occlusion rate 87.1% Occlusion factors: Women RR = 0.19 (95% CI; 0.09 – 0.41) p < .0001 Catheter size 6F vs 8FR RR = 0.71 (95%CI; 0.43 – 1.25) *p* = .28 Tumescent fluid (> 250 ml) RR = 0.59 (95%CI; 0.34 – 1.02) *p* = .06
Weiss 2002 Maryland, US (71)	120 p (140 Legs)	▪ Vein occlusion on duplex ultrasound at 1 week,, 6 weeks, 6 months, 1 year and 2 years	1 week 98% (137/140) occlusion no flow 6 weeks 4% (5/140) flow	3% (3/98) recanalized At 2 years, 90% (19/21)treated vein completely absent
Welch, 2006 Maryland, US (76)	146 p (184 Legs)	▪ Vein occlusion on duplex ultrasound at 1 week,, 2-3 months	1 week 77.7% (143/184) completely occluded partial patency (12 limbs with <10 cm patency, 17 limbs patency > 10 cm 3.8% (n = 7) totally patent, all with 6F catheter	-

Mafrini – Endovenous Reflux Management Group 2000 Italy, Sweden, US ,UK (59)	142 p (151 Legs, 152 veins) with ClosurePlus catheter	▪ Occlusion of treated vein on duplex ultrasound at 1 week, 6 weeks, 6 months, 12 months ▪ Closure catheter mean F-Up 4.7 months ,Restore catheter mean F-UP	1 week C;losure catheter 93% (141/151) No flow no reflux Closure at mean 4.7 mo F-UP 6% recurrent reflux rate and 4% incidence recurrent varicities
VNUS Closure Treatment Study Group			
Merchant – Closure Group 2005 (61)	Sub-cohorts of VNUS Closure Study Group - 5 yr-results – Treated before October 2004 at 34 centers 1,006 p (1,222 legs) – 12 centers contributed 5-yr data	▪ Vein occlusion on duplex ultrasound at 1wk, 6 months, 1, year, 2 years, 3 years, 4 years, 5 years ▪ Vein occlusion defined as no evidence of flow from 3 cm below the SFJ along the length of the treated vein ▪ Reflux defined as any evidence of reverse flow > 0.5 seconds in any treated vein segment or in the SFJ area (or SPJ)	1 week 96.8% vein occlusion (1,222 VAR and 985 available for follow-up)

GSV refers to the great saphenous vein; SSV, small saphenous vein; VAR, veins at risk

Factors Affecting RFA Treatment Effectiveness

The need for concomitant SFJ ligation with RFA was examined in two reports. (62;72). In the Boros et al. study (72), procedures were performed at one center by one of three board-certified vascular surgeons with different ligation preferences – one always, one never and one selectively performing ligation. The mean age and gender was similar in the two patient groups but the rate of diabetes was higher [11% vs 3% (p = .0367)] in the group not receiving ligation. Successful vein ablation was reported to be higher (92% (71/72), but not statistically higher (p = .096) for patients receiving SFJ ligation than those not receiving ligation (84% (119/142).

In the multicenter VNUS Study Group patients were treated, based on surgeon preference, without and with surgical ligation of the SFJ through a groin incision. The SFJ ligation was generally performed as a complete dissection of the SFJ to reveal and ligate the junctional tributaries. The contribution of the surgical ligation to RFA success was examined in the Chandler at al. report (62) in which the first 60 legs treated with high ligation were compared with the first 120 legs treated without high ligation. The incidence of recurrent reflux (2% vs 8%; p = .273 and varicose veins (6% vs 4%; p = .687) were similar between the two groups at 6-month follow-up suggesting that there was little incremental gain with the addition of SFJ ligation. The study however was not powered to detect differences in recurrence rates of 10% or less.

The treatment effectiveness of RFA ClosurePlus catheter for saphenous vein diameters > 12 mm was examined in the 4-yr follow-up report for a patient subgroup of the multicenter VNUS Study Group. (64) In the study report of the 858 treated veins, 58 were veins with a diameter > 12 mm (mean diameter 14.5 mm ± 2.1 mm). The occlusion rate for the 40 patients that were followed 1- week post-procedurally was 97.5% (39/40) and for the 28 patients followed at 6 months, the occlusion rate was 96.6% (28/29).

ClosureFast - RFA Second Generation Catheter

Two studies (three reports) (78-80) were identified with RFA procedures performed with the second generation catheter the Catheter Fast which also uses the principle of segmental thermal ablation in the saphenous vein (see Table 5). In these studies there was no vein diameter restriction for RFA ablation. The clinical reports for this RFA experience involve a single site in the United States (78) and two reports (79;80) on a large European multicenter prospective registry cohort study (ClosureFast Clinical Study) conducted at eight sites in Germany and France.

The European multicenter trial involving eight sites in Germany and France was the first group to evaluate the feasibility, safety and effectiveness of the ClosureFast catheter. Procedures were performed in outpatient setting under tumescent anaesthesia and concomitant procedures such as phlebectomy (71.4% cases) and foam sclerotherapy for tributaries (13.9% cases) were performed. The study cohort consisted of 194 patients (252 legs) without vein diameter restrictions. Clinical and imaging follow-up conducted at 72 hours, 3 and 6 months was completed for 100% (194/194), 81% (132/163) and 85.5% (53/62 of patients eligible at the follow-up time .

Vein occlusion and reflux free rates by Kaplan Meir estimates were 99.6% at 6 months. Significant symptom relief was observed as early as 3 days post-operatively. However, it was noted that improvement of oedema may also have occurred because of subsequent wearing of compression stockings. Prior to the intervention, 28.2% wore compression stockings and post-operatively at day 3, 3 months and 6 months, 97%, 14% and 9.7% at 6 months wore compression stockings. The mean VCSS score improved from 3.9 ± 2.0 at baseline to 0.9 ± 1.6 at 3 months and to 1.5 ± 1.8 at 6 months.

In the US trial (78) the objective was to evaluate whether or not treatment effectiveness of the ClosureFast catheter differed for larger GSV target vein diameter (> 12 mm). The experiences of two surgeons at a single center conducting RFA with the Catheter Fast RFA device were evaluated on a consecutive group of 310 patients (342 saphenous veins) over an eighteen-month study period. All procedures were performed in an outpatient setting with tumescent anaesthesia. Successful treatment defined as closed vessels with no vein segments open in the treated area, was compared in veins that were in the indicated vein diameter for RFA ablation (Group A ≤12 mm) to those that were greater (Group B > 12 mm) than the vein indication region. The study included 246 patients (210 GSV, 36 SSV) in group A and 96 patients (88 GSV,8 SSV) in group B . Imaging and clinical follow-up was conducted postoperatively between 2 and 5 days in 100% of the subjects and at 6 months in 43% (155/342). Complete vein closure rates post-operatively were 94% in Group A and 96% in Group B the larger vessel group. Technical failure, unable to place an access sheath due to spasm occurred in four patients (all with smaller diameter veins). Complete closure rates in the sub groups evaluated at 6 months were seen in 98% of Group A and 100% of Group B.

Table 5: Imaging Follow-Up and Outcomes of RFA Ablation of Great Saphenous Vein with ClosureFast Catheter

Author, Year, Country	Sample	Treatment Success, Follow-UP	≤ 3 Months	6 Months
Calcagno 2009 Pennsylvania, US (78)	246 GSV (<12 mm), 96 GSV (≥ 12 mm)	▪ Occlusion of treated vein on duplex ultrasound at 2 wks and at 6 months ▪ Closure defined as no vein segments open in the treated vein, partial closure defined as vein with some closed and some patent sections and patent was a vein open on ▪ Mean follow-up of *4 months (range: 2 - 11 months)*		Complete closure for 98% (n=112) for veins ≤ 12mm and 100% (n=43) for veins > 12mm. Follow up was unavailable for 46% and 45% of the two groups
ClosureFast Study Group				
Proebstle 2008 Germany, France – ClosureFast Study Group (80)	April – November 2006 at 8 sites -194 p (252 Legs)	▪ Occlusion and lack of vein reflux on duplex ultrasound at 1 week, 3 months, 6 months. ▪ Occlusion defined as absence of flow from 3 cm inferior to SFJ along treated vein	Occlusion rates 99.6% 81% (132/163) of patients eligiblefor 3-month follow-up were imaged	Occlusion rate 99.6%(85.5% of patients eligible for 6-month follow-up were imaged
Creton 2010 Germany, France ClosureFast Study Group (79)	April 2006 – March 2007 at 8 sites – 225 p (295 Legs)	▪ Occlusion and lack of vein reflux on duplex ultrasound at 3 days, 3 months, 6 months and 1 year.		Occlusion rate 98.6% at 6 months and 96.9% at 1 year 289 examined at 6 months and 220 at 1 year (75% of treated legs)

DU refers to Duplex ultrasound: SSV, small saphenous vein; VAR, veins at risk

2B. Safety of Radiofrequency Ablation

The reporting standards for adverse events after endovascular laser ablation recommended by both the Society Interventional Radiology and the Society Vascular Surgery were adopted for this report. (17) Complications or adverse events following RFA in the GSV cohort studies are listed in Appendix 2, Table A3. For this evidence review, major adverse events were defined to include vascular events such as deep venous thrombosis (DVT), pulmonary embolism (PE), infection, nerve damage, or skin burns. Other events requiring additional care or hospitalization were also considered major adverse events. Minor complications such as pain and bruising frequently occur following RFA but are generally of short duration and self limiting without clinical sequaelae. Other complications such as hematoma were often cited as complications but were more likely related to secondary or concomitantly performed procedures such as phlebectomy than to the primary RFA treatment. Such minor complications are not generally included as major events unless they result in additional care or hospitalization.

The major adverse events reported in RFA cohort studies are summarized below in Table 6. The entire patient experience in the reported cohort studies is summarized below and includes 3,664 patients (4,326 legs) and represents:

- Ten cohort studies with RFA Catheter Plus device (1,944 patients, 2316 legs)
- Two European international multicenter cohort studies, the VNUS Closure Treatment Study Group and the Endovascular Study Group with RFA Catheter Plus catheter (1216 patients, 1373 legs)
- Two cohorts studies with the RFA Catheter Fast catheter (504 patients, 594 legs).

The overall major adverse event rate for RFA based on this reported patient experience was 2.9% (105/3664).

Table 6: Major Adverse Events After RFA Ablation in Great Saphenous Vein

Event	Number of AE Occurrences	Percent	Rate of Occurrence
DVT	67/3,664	1.8%	< 2 in 100
Infection	16/3,664	0.44%	< 5 in 1,000
Skin Burns	11/3,664	0.30%	< 1 in 1000
Nerve Damage	10/3,664	0.27%	< 3 in 1,000
PE	1/3,664	0.02%	< 3 in 10,000
Overall Major AE	105/3,664	2.9%	< 3 in 100

AE refers to adverse events; DVT, deep venous thrombosis; PE, pulmonary embolism

Major thrombotic adverse events such as PE were only reported in one study, (0.1%; 1/858) in the VNUS collaborative study. (63) The occurrence of DVT was the most common major adverse event (1.8%) reported in the cohort studies. DVT, however, was variably defined and this adverse event rate varied (range 0.2% to 16%) across the six studies reporting these events: 0.2%, 1/633 (70), 0.5%, 4/858 (64). 3.5%, 3/86 (59), 4% (72), 13% (66) and 16%, 12/73 (75). In the VNUS closure registry study, the 0.5% occurrence of DVT was defined to include localized thrombus formation at the SFJ that extended no more than 10% into the common femoral vein. In the Puggioni et al. study (66) DVT was reported as any thrombus protrusion into the SFJ (24, 8%), common femoral vein (12, 5%), and into the calf vein (7, 2.5%). No DVT events were reported in the studies involving the Catheter Fast RFA catheter.

Skin burns involving three cases (1.4%, 3/2100) with full thickness burns, were reported in one study. (59). In that study (VNUS Closure study group) the occurrence of skin burns was reported to be related to

the experience of the operators in the trial. (64) In the early cases, a 4.2% (6/143) rate of burns was reported and none were reported in the subsequent 143 cases. In a later second report from the VNUS study group involving 484 treatments, a 1.7% burn rate was reported. A rate of 0.5% burn rate was also reported for RFA procedures performed after the introduction of tumescent anaesthesia.

Paresthesia (numbness) or dysesthesia (altered sensation), usually confined to the thigh along the course of the treated vein was frequently reported in the cohort studies. Saphenous or sural nerve damage was rarely (0.27%) reported in the studies. Paresthesia persisting beyond 6 months would be an increasing concern for permanent nerve damage but follow-up in the studies rarely continued beyond 6 months. In the Manfrini et al. (59) report, at 6 months 13 of the 16 patients followed for paresthesia after the procedure, still had paresthesia and at 1 year of the five patients continued to be followed, three (1.4%, 3/210) had persistent saphenous or sural nerve paresthesia. Paresthesia rates were also reported to be higher before the introduction of tumescent anaesthesia.

Factors affecting patient safety were the primary study objectives of RFA ablation in two trials. (66;67) In the Tzillinis et al. study (67) the safety of RFA was evaluated in an older (Group 1,≥ 70 years) versus younger (Group 11,< 70 years) patients. The concern was that elderly patients because of their advanced age, co-morbidity and increased risk for anaesthsia, might be at "high risk" for the procedure. There were 386 patients (449 legs) in the younger group (mean age 47 years ± 11) and 35 patients (41 legs) in the older group (mean age of 75 years ± 4). Procedures were performed in ambulatory setting under regional or general anaesthesia with tumescent anaesthesia. The majority of patients (97%) were discharged the same day.

Indications for treatment in the older patient group were for active or healed ulcers (9 legs), stasis dermatitis (8 legs), oedema with leg pain (2 legs) and painful varices (22 legs). In the younger patient group, the indications were for ulceration (28 legs), lipodermatosclerosis (46 legs), painful oedema (13 legs) and symptomatic varicoses (362 legs). Elderly patients had significantly worse CVI and were four times more likely than younger patients to be treated for ulceration and twice as likely to be treated for stasis dermatitis. There were no perioperative deaths, or cardiac, renal, respiratory complications and no patients were hospitalized for any procedural related complications. All active ulcers in both groups healed within 6 weeks of the procedure

In the Puggioni et al. (66) study, the safety of RFA in patients with prior venous thrombotic events was evaluated in 274 patients (293 legs). Evidence of a prior DVT was found in 10% (29/293) of the limbs. The procedures, performed with three surgeons at one site were initially performed under general or spinal anaesthesia (167 legs) and later changed to outpatient office based under local and tumescent anaesthesia. Concomitant procedures included phlebectomy and all procedures were performed with tumescent anaesthesia and with no vein diameter restrictions.

After RFA treatment, acute thrombotic events (AT) occurred in 13% (38/293 legs) of patients and included thrombus protrusion into the SFJ (8%, 24 legs), common femoral vein thrombus (2.5%, 7 legs) and calf vein thrombus (2.5%, 7 legs). AT events, all identified on duplex follow-up, occurred in 7% (2/29) of those having prior DVT and 14% (36/264) without prior DVT (p = .36). AT events were treated with standard anticoagulation and eight patients received a IVC filter (5 permanent, 3 temporary). Complete resolution of the thrombus occurred within two months in (mean 15.5 days, range 2 – 60 days) in 30 of the 36 cases. Pain and oedema developed in two of these patients suggestive of post-thrombotic syndrome. Thrombus resolved in all the patients (n = 8) receiving an IVC filter. No clinically significant PE or other postoperative complication occurred in the study group. In multivariate analysis only larger proximal GSV (p = .049) and prior superficial thrombophlebitis (p = .0135) were independent risk factors for the occurrence of DVT.

2C. Randomized and Controlled Studies Involving RFA

Thirteen studies [eight RCTs and five controlled clinical trials (CCT)] involving RFA treatment for varicose veins were identified in the MAS evidence review. The clinical trials were divided into two groups based on the treatment comparator to RFA.

Group A: RFA versus surgical ligation and vein stripping (5 RCT (81-88), 1 CCT (89),

Group B: RFA versus endovascular laser ablation (3 RCT (90-92), 5 CCT (66;93-96)

The methodological details of the studies including design, conduct and evaluation are outlined in Appendix 2, Table A4**.** Trial outcomes were reported using the standardized Consort format in three trials. (83;85;88) The primary and secondary outcomes for the clinical trials are summarized in Appendix 2, Table A5. The outcome measures included validated measures for symptom and HRQOL improvement with both generic and vein disease specific instruments. The outcomes reported in the clinical trials were grouped as being either: technical, anatomic/functional, clinical or patient related (see Table 7).

Group A: RFA versus Surgical Ligation and Vein Stripping

Five RCT studies conducted in six countries compared RFA to surgical ligation and stripping of the GSV (as outlined in Appendix 2**,** Table A6). One of the trials involved a within-subject paired design for recurrent bilateral VV. (81) All but one trial (86) involved two treatment arms. The Stotter et al. trial (86) involved three treatment groups: Group 1 underwent RFA and Group 2 and 3 underwent different surgical approaches, inversion and cryostripping, to GSV vein stripping. The trials involved in total 292 patients, 142 treated by RFA and 150 treated by surgical ligation and vein stripping. Patient ages ranged from 33 to 54 years and involving a high proportion of females (range 69% to 93%).Vascular surgeons performed both the surgery and RFA ablations in all the clinical trials and treatments were performed in the operating theatre under general anaesthesia in all trials. Tumescent anaesthesia with regional or general anaesthesia was only employed in one trial. (82) The Closure System with the first generation catheter the ClosurePlus was employed for the RFA treatment arms in all trials. Technical limitations with this catheter involved restrictions based on for vein diameters and GSV $\geq$ 12 mm were an exclusion criteria for all trials.

The interventions in the trial arms were similar across the trials. RFA treatment alone was compared to surgical ligation and stripping of the GSV in all the trials. Concomitant phlebectomies for tributary varices were performed in both treatments arms in all studies except the Stotter et al. trial. (86) Concomitant interventions (usually phlebectomy or ligation of tributary varices) reflected the desire to avoid under treating patients and requiring them to return for subsequent additional interventions. The surgical stripping techniques included standard forward stripping in the trials and in the Stotter et al. trial, two different surgical approaches to vein stripping were compared – the standard stripping versus cryostripping.

Table 7: Clinical Trial Reported RFA Outcomes and Endpoints

Study	Technical				Anatomic - Functional			Clinical		Patient Satisfaction	Vein Disease specific QOL	Generic QOL	Costs
	Procedure	Pain	Recovery	Complications	Patency Recanalization / Neovascularize	Vein Reflux *	Varicosities	Vein Symptoms	Cosmesis				
RFA vs. Surgery													
Hinchliffe , 2006 (81)	✓	✓		✓	✓								
Kianifard, 2006 (89)					✓	✓							
Lurie, 2003, 2005 (82;83)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		
Rautio, 2002 Perala, 2005 (84;85)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Stotter, 2006 (86)	✓	✓	✓	✓	✓	✓			✓	✓	✓		
Subramonia, 2008, 2010 (87;88)	✓	✓	✓	✓	✓	✓		✓		✓	✓		✓
Endovascular RFA vs. Laser Ablation													
Almeida, 2009 (90)		✓	✓	✓	✓			✓			✓		
Morrison, 2005 (91)	✓	✓		✓	✓								
Shepherd, 2010 (92)		✓	✓	✓				✓			✓	✓	
Almeida, 2006 (93)				✓	✓								
Marston,, 2006 (95)				✓	✓			✓					
Puggioni, 2005 (97)	✓			✓	✓	✓	✓						
Shepherd, 2010 (96)		✓											

*Recanalization Neovascularization

Operative Time and Technical Success

The durations for the treatments are summarized below in Table 8. In three of the trials (85;86;88), mean procedure time and total theatre time was significantly longer for RFA than for surgery. In the Subramonia et al. trial (87) significant differences in treatment duration (95% confidence interval) were reported to be 24 to 35 minutes in procedure time and 22 to 33 minutes in operating room time. In the Lurie et al. trial (82) however, the procedure time was shorter for the RFA group than the surgery group (74 ± 10 minutes versus 89 ± 12 minutes). In that trial, variability in reporting procedure times across the multiple study sites was an acknowledged study limitation. In the Hinchliffe et al trial (81) which involved treating bilateral recurrent disease with RFA in one leg and surgery in the other, procedure time was quicker for RFA than for surgery (25.5 versus 40 minutes).

Table 8: Procedural Times for RFA and Surgical Ligation and Vein Stripping

Author	Treatment	RFA Time Minutes ± SD	Surgery Time Minutes ± SD	Procedural Time Difference Significance
Hinchliffe, 2006 N = 16 pairs, (81)	Median Procedure Time	25.5. (Range 20.5 – 31.3)	40.0 (Range 34.5 – 45.5)	*RFA < Surgery* *P* = .02
Lurie, 2003 N= 43,36 (82)	Mean Closure Time	41.5	NR	NR
	Mean Total Treatment Time	74 ± 10	89 ± 12	RFA < Surgery NR
Rautio, 2002 N= 15,13 (85)	Mean Procedure Time	75 ± 16.6	57 ± 11.0	RFA > Surgery *p* = .003
	Mean Theater (OR) Time	115 ± 18.3	99 ± 12.9	RFA > Surgery *p* = .01
	Mean Recovery Room Time	227 ± 57.6	198 ± 40.7	RFA > Surgery *p* = .16
Stotter, 2006 N = 20,40 (86)	Mean Procedure Time	51	21 (invagination stripping) 19 (cryostripping)	RFA > Surgery *p* NR
Subramonia, 2009 N= 48,45 (88)	Mean Procedure Time	76.8 ± 14.5	47.0 ± 10.8	RFA > Surgery *p* < .001
	Total Theater (OR) Time	83.6 ± 14.5	55.7 ± 10.9	RFA > Surgery *p* < .001

NR refers to not reported; OR, operating room

Recovery and Post Procedural Complications

Four trials (82;85;86;88) compared the recovery of patients undergoing RFA or surgical ligation and vein stripping (summarized in Table 9). Procedures in all trials were performed in the operating theatre and general anaesthesia was used in both treatment arms. In the Lurie et al. trial (82), anaesthesia choice varied by trial site and included general anaesthesia or regional local anaesthesia with tumescent

anaesthesia.

In all trials, recovery measured by return to usual activity or return to work, was significantly faster after RFA than after surgery. In the RFA treatment groups, recovery as measured by return to usual activity also varied between trials with the method of anaesthesia. Those employing tumescent anaesthesia with RFA had a quicker recovery time to normal activity (1.15 days, (82), 3.0 days (88)) than those not using this form of anaesthesia (6.5 days (85), 7.0 days (86)). In the Lurie et al. trial (82), the use of tumescent anaesthesia in the surgical group also significantly improved recovery time after surgery (3.89 days) compared to recovery time for surgical groups reported in other studies (15.6, 14 days, 12.5 days) employing general anaesthesia . In the RFA group, patients undergoing the treatment with general anaesthesia were much more likely to return to usual activity the same day after treatment than the surgical group under general anaesthesia (33% versus 9%). All of the RFA patients returned to usual activity within 1 to 3 days compared to 41% in the surgical group.

Table 9: Recovery after RFA or Surgical Stripping for Varicose Veins

Author	Anaesthesia for RFA	Anaesthesia for Surgery	Recovery for RFA	Recovery for Surgery	Recovery Difference
Lurie 2003, 2005 France, Austria, United States (82;83)	Regional or local anaesthesia (includes tumescent) 73% or general anaesthesia (27%) preference by site (n=5)	Regional or local anaesthesia (includes tumescent) 47% or general anaesthesia (53%) preference by site (n=5)	Mean return to normal activity duration 1.15 days (95% CI, 0.05 – 2.34)	Mean return to normal activity duration 3.89 (95% CI, 2.67 – 5.12)	RFA < Surgery p = .02
			Mean return to work duration 4.7 days (95% CI, 1.16 – 8.17)	Mean return to work duration 12.4 days (95% CI, 8.66 – 16.23)	RFA < Surgery p < .05
Rautio 2002 (85) Perala , 2005 (84) Finland	General anaesthesia Tumescent anaesthesia not used	General anaesthesia	Mean sick leave duration 6.5 days SD 3.3	Mean sick leave duration 15.6 days SD 6.0	RFA < Surgery p < .001
			Patient assessment sick leave duration 6.1 days SD 4.4	Patient assessment sick leave duration 19.2 days SD 10.0	RFA < Surgery p = .001
Stotter 2006 Germany (86)	General anaesthesia Tumescent anaesthesia not used	General anaesthesia	Mean return to normal activity 7 days	Mean return to normal activity 14 days invagination stripping, 12 days cryostripping	RFA < Surgery p = 0.021
Subramonia 2009 United Kingdom (87)	General anaesthesia with local tumescent anaesthesia	General anaesthesia	Median return to normal activity 3 days IQR 2 - 5 days	Median return to normal activity 12.5 days IQR 4 - 21 days	RFA < Surgery *95% CI -11.61, -4.23* p < .001
			Median return to driving 4 days IQR 2 - 6 days	Median return to driving time 7 days IQR 5 – 12.5 days	*95% CI -6.82, -2.19* p < .001
			Median return to work time 10 days IQR 4 – 13 days	Median return to work time 18.5 days IQR 11 – 28 days	*95% CI -12.95, -2.21* p = .006

IQR refers to interquartile range; RFA, radiofrequency ablation

Safety

The major adverse events reported in the RCT trials for RFA and surgery are outlined in Table 10. The overall major complication rate based on the pooled adverse events from all the trials was 6.3% (9/142) in the RFA group and 11.3% (17/150) in the surgery group. All of the trials except one (84) reported on complications occurring in the immediate post-operative period. There were no DVT or PE's for either treatment group reported in any of the trials. Thermal skin injury was reported in one trial (85) for the RFA group (1/142). Infections, related to incision wounds, were mainly reported in the surgical groups (3.3%; 5/150). In the one study (82) where vein access in the RFA treatment group was achieved through a surgical cut down in the groin rather than a percutaneous approach in almost half of the cases, wound thrombosis occurred almost as often in the RFA group (7.0%; 3/43) as the surgical group (11.1%; 4 /36).

Saphenous nerve injury, another potential major adverse event was reported more commonly in the surgery groups (5.3%; 8/150) than the RFA groups (2.4%; 1/142). Only one study, however, reported on complications in longer term follow-up and symptoms related to saphenous nerve injuries were reported in both the RFA (1/15) and surgery (5/13) treatment groups. Paresthesia or dysesthesia was reported in both treatment groups in the short term. In one study (82) paresthesia was reported to be much higher in the RFA than the surgery group (22 versus 9 cases). In the Subramonia et al. trial (88), paresthesia was evaluated longitudinally after treatment and was shown to be a function of the post-operative follow-up time period. Follow-up reports in these trials, except for the Perala et al. report, were all within 3 months.

Table 10: Major Adverse Events in RCT of RFA vs. Surgery

Author, Study Size (RFA, Surgery)	Follow-Up	RFA Major Adverse Events*	Surgery Major Adverse Events
Hinchliffe et al., 2006 N = 16 pairs, recurrent VV	6 week F-UP	0	1 superficial post-operative wound infection 1 persistent thrombophlebitis
Lurie et al., 2003, 2005 N = 43, 36	3 week F-Up	3 surgical wound thrombosis	4 infections 4 surgical wound thrombosis
Rautio et al., 2002 N = 15, 13	2 month F-Up	3 clinical thrombophlebitis 1 thermal skin injury	0
Perala et al., , 2005 of Rautio's trial	3 Yr F-Up	1 saphenous nerve injury 1 extended period superficial thrombophlebitis	5 saphenous nerve injuries
Stotter et al., 2006 N = 20, 40	6 Week F-Up	0	0
Subramonia et al., 2009 N = 48, 45	5 week F-Up	0	0
Total = 292 (142,150)		9 (6.3%) 95% CI; 3.4% - 11.6%	17 (11.3 %) 95% CI; 7.2% - 17.4%

*Major adverse events include deep venous thrombosis,, pulmonary embolism,, thermal injury, or saphenous vein injury

Imaging Defined Outcome after RFA Ablation of Great Saphenous Vein

All five RCT studies reported some measure of duplex ultrasound defined measures of treatment effectiveness, usually as vein closure or absence of the treated vein. The surgical approach was similar in all the studies except in the Stotter et al. trial (86) in which two surgical approaches to vein stripping were compared – traditional invagination stripping versus cryostripping. In all the trials the ClosurePlus catheter was used in the RFA treatment arm and due to limitations of the catheter design was restricted to saphenous vein diameters < 12 mm. The RFA treatment arms were similar with respect to procedural protocols, temperature settings and pull back rates. Co-interventions such as phlebectomies were generally performed for additional varices in both treatment arms in all studies except the Stotter et al. trial (86) where no concomitant procedures were performed.

Intra-operative Success and Short Term Effectiveness

Immediate technical success or treatment efficacy was reported in four trials (81;82;85-87) and results are summarized below in Table 11.

In the Hinchliffe at al. trial (81) intra-operative technical success was not reported but ultrasound follow-up at 6 weeks in legs undergoing RFA ablation for recurrent VV demonstrated complete occlusion in thirteen (81.3%) legs and partial occlusion in three legs. Persistent incompetent accessory truncal veins were also noted in three legs. In the surgical treatment group, of the 16 legs undergoing surgical stripping, fourteen (87.5%) were completely stripped and two were partially stripped.

In the Lurie et al. trial (82) intra-operative technical success in the RFA group was reported to be 95% (42/44) with two inadequate treatment failures. In the surgical ligation and stripping group, 100% (36/36) of the GSV's were successfully stripped. At 72 hours flow in the proximal GSV was detected in seven legs (16.3%), four legs left with open segments were considered technical incomplete closures. In the surgical group, there was no reflux in the 36 legs followed at 72 hours and at 1 week.

In the Rautio et al. trial (85) the intra-operative technical success was reported to be 100% in the RFA with no flow in the treated veins. In the surgical group, one case or reflux in the accessory branch of the GSV was reported.

In the Stotter et al. trial (86), the intra-operative technical success in the RFA group was 95% (19/20) with one GSV partially and temporarily open segment. In the surgical groups, vein stripping was 100% in the invagination group and 90% in the cryostripping group – two cases were left with residual GSV segments.

In the Subramonia et al. trial (87) the intra-operative technical success in the RFA group was 95.7% (45/47). In two cases there was spontaneous flow and the procedure needed to be repeated. Additional technical complications were also reported for the RFA group. Tumescent administration was unsuccessful in two cases due to venous spasm and poor visibility and GSV perforation occurred in three cases. The accumulation of thrombus on the catheter during the procedure necessitated the removal of the catheter in nine cases. In the surgical group, 15.6% of the cases (7/45) involved incomplete stripping. At 5 weeks, the GSV was visualized with no flow in all patients in the RFA group. The seven patients with incomplete stripping had varying degrees of segmental reflux; one with brisk reflux, two with no flow and four with trickle grade flow.

Table 11: Intra-operative RFA Success and Short Term Effectiveness

Author, Year	Intra-operative Effectiveness		Post-operative Effectiveness	
	RFA	Surgery	RFA	Surgery
Hinchliffe et al., 2006 ,	NR	NR	Complete occlusion in 13 legs (81.3%) and partial occlusion in 3 legs at 6 weeks	14 legs completely stripped (87.5%) and 2 partially stripped at 6 weeks
Lurie et al., 2003	95% (42/44)	100% (36/36)	84% (36/43) complete occlusion - flow in the proximal GSV in 7 legs and 4 legs (9.3%) left with open segments	Reflux free in all legs 100% (36/36) at 1 week
Rautio et al., 2002	100% (15/15)	1 case of reflux in the GSV accessory branch	NR	NR
Stotter et al., 2006	95% (19/20), one partially and temporarily open segment	100% (20/20) invagination 90% (18/20), two residual GSV segments	Treated GSV invisible on ultrasound in all (N=19) limbs, 11% (2/19) segmental recanalization at 6 weeks	Groin neovascularization occurred in 1 case cryo strippingR
Subramonia et al., 2009	95.7% (45/47)	Complete stripping in 84.4% (38/45) - 7 cases with incomplete stripping	GSV was visualized with no flow in all patients at 5 weeks	The 7 patients with incomplete stripping, had varying degrees segmental reflux at 5 weeks

Longer Term Effectiveness

Longer term imaging outcomes were reported in three trials at 1-year (86), 2-year (82) and 3-year (82;85) follow-up.

In the Stotter at al. trial (86) segmental recanalization (< 10 cm) occurred in 10.5% (2/19) in the RFA group at 1-year follow-up,. The treated portion of the GSV, which was at ten cm below the SFJ region, was ultrasonographically invisible at 1 year. No recanalization occurred in the surgical groups. No groin vascularisation was noted in either group.

In the Lurie et al. trial (83), the overall rate of GSV patency at 2 years was 13.9% (5/36). Three patients had patent GSV's (two with reflux) and in two other patients the GSV had recanalized. In the other patients the GSV vein diameters showed increasing and significant reductions in diameter on imaging follow-up. In the surgical group, 10.3% (3/29) had open incompetent reflux. Neovascularization at the SFJ was detected in 2.8% (1/36) patient in the RFA group and in 13.8% (4/29) in the surgical group. Recurrent varicose veins at 2 years were detected in 14.3% of the RFA group and 20.9% of the surgical group ($p > .05$).

In the Perala et al. trial (84) at 3-year follow-up, the surgeon clinically detected recurrence was higher but not significantly ($p = .40$) in the RFA group (33%, 5/15) than in the surgical group (15%, 2/13). Recurrence as reported by patients was also higher ($p = .065$) in the RFA group (27%, 4/15) compared to the surgical group (15% , 2/13). Recurrence due to reflux, recurrent or residual varices occurred in five patients (33.3%) in the RFA group. It was noted that none of the original occluded GSV segments were recanalized. The overall rate of GSV patency at 2 years was 13.9% (5/36). The emergence of small superficial branches in the SFJ area occurred in one patient (7%) in the RFA group and one (8%) in the

surgical group. One patient in each group underwent re-operation for recurrent varicose veins.

Vein Symptom Improvement

The impact of RFA and surgery on venous clinical symptoms was compared using validated instruments in three trials (83;84;87). In all trials, venous clinical symptoms in both treatment groups were significantly improved over baseline but at different follow-up points - at 5 weeks (88), at 2 years (83) and at 3 years (84).

In the Subramonia et al. trial (88) vein symptoms based on two measures of venous symptom improvement, the Total Clinical Severity Score (TCSS) and the Venous Disability Score (VDS), were reported to be improved at five weeks follow-up. At baseline, the majority of patients in the RFA (78.7%, 37/47) and surgery (83%, 34/41) groups had TCSS scores of 1or 2 and the majority of patients in each treatment group had VDS scores of 1 at baseline. Three quarters of the patients in each group were reported to have improved TCSS and VDS scores after intervention (follow-up mean scores not reported). Two patients, one in each group had a worsening VDS score.

In the Lurie et al. trial (83) the mean pre–operative TCSS scores were > 4.0 in the RFA and surgery groups and steadily decreased over time in both groups and at 1 and 2-year follow-up, the mean TCSS scores in both groups were < 1.0 (score values not reported). At 2-year follow-up, 33% (12 patients) in the RFA group and 28% (8 patients) showed no signs of venous disease based on their CEAP scores.

In the Perala et al. trial (84) the mean decrease in VCSS scores at 3 years was 4.3 (SD, 2.3) in the RFA group and 4.0 (SD, 1.2) in the surgery group and the differences in improvement between groups was not significantly different ($p = 0.7$).

Impact on Health Related Quality of Life

The impact of RFA and surgery on Health Related Quality of Life (HRQOL) of patients undergoing treatment for symptomatic varicose veins was evaluated in four trials. (83;85;86;88), Only one of the trials (83) evaluated the impact of RFA and surgery on HRQOL beyond the short term post-operative period.

In the Stotter et al. trial (86) the Chronic Venous Insufficiency Quality of Life measure (CIVIQ2), a vein disease specific HRQOL questionnaire was used to evaluate the impact of RFA and surgery on HRQOL. The CIVIQ2 scale ranges from 0 representing least impact on QOL and highest QOL to 100 the maximum impact on QOL. After 6 weeks follow-up, the mean cumulative impairment score was significantly ($p = .012$) better for RFA (2.8) than for invagination stripping (7.9) of cryostripping (17.1).

In the Subramonia et al. trial (88) HRQOL was measured at 5 weeks post treatment by two vein disease specific instruments, the Aberdeen Varicose Vein Symptom Score (AVVQ) questionnaire and the VEINES-QOL/Sym questionnaire (V-Q/Sym Q). The mean AVVQ score was significantly improved in both RFA (9.12) and surgery (8.24) groups. The difference in mean improvement between the treatment groups (95% CI; -3.64 to 1.89) was not significant ($p = 0.532$). Vein symptoms improved in both treatment groups. The V-Q/Sym Q mean score was also significantly improved for both RFA (12.62) and for surgery (9.94). The between group difference in symptom improvement was not significant (95% CI; -1.65 to 7.01; $p = .220$).

In the Rautio et al. trial (85), the SF-36 a generic measure of HRQOL, was reported at 1 and 3 weeks follow-up. Significant improvements in physical functioning were noted in both treatment groups although improvements occurred faster in the RFA treatment group. None of the changes in the individual or global measures of HRQOL at 1 or 4 weeks were significantly different between the two treatment

groups.

In the Lurie et al. trial (83), the early postoperative improvements over baseline in HRQOL global measure evaluated with CIVIQ2 and pain score, presented graphically, were significantly better ($p < .05$) in the RFA group than the surgery group at 72 hours and at 1 week follow-up. Global HRQOL scores continued to improve over time in both groups and at 1 and 2-year follow up were significantly better for the RFA than for surgery group (group mean data not reported).

Patient Satisfaction

Three clinical trials (84;86;88) reported patients' satisfaction with treatment for their VV either by RFA or by surgical ligation and stripping.

In the Subramonia et al. trial (88), patient satisfaction was rated on a 10-cm linear visual analogue scale and reported as median values with interquartile ranges (IQR) at 5 weeks follow-up. Satisfaction was also based on the patient's willingness to recommend the treatment to others and by their willingness to undergo the same treatment on the opposite leg if required. Patient satisfaction (median VAS score) at 5 weeks was significantly ($p = .016$) better with RFA (10, IQR 8.4 to 10) treatment than with surgery (8.5, IQR, 7.5 to 10). Significantly ($p = .005$) more patients were also willing to recommend the RFA (97.9%; 46/47) procedure than surgery (78%; 32/41). Dissatisfaction in both treatment groups was commonly with postoperative morbidity including pain, discomfort and restricted mobility. No patient in either treatment group reported complete dissatisfaction with the procedure.

In the Stotter et al. trial (86) patient satisfaction with their operative procedure and with the cosmetic appearance of their lower extremities was rated on a 1-10 VAS scale. At 1-year follow-up patients in the RFA group were significantly more satisfied overall with their operative procedure ($p = .001$) and with the cosmetic appearance of their legs ($p = .006$) than patients were in either surgical group.

In the Rautio et al. trial (85) patients were asked about their satisfaction with treatment at 8 weeks following treatment. All patients reported being satisfied with their treatment although one patient in the RFA group and four in the surgery group were dissatisfied with the cosmetic appearance of their lower extremities. At 3-year follow-up (84), all but one patient (7%) in the RFA group and two patients (15%) in the surgical stripping were not satisfied with their treatment. All patients enrolled in the study groups would have suggested the procedure to a relative or a friend.

Patient Preference

Patient preference either for RFA or surgical treatment was evaluated through clinical trial participation rates and patient surveys. Recruitment information for trials indicating patient willingness to undergo randomization was reported in three RCT studies of RFA versus surgery. (82;85;88)

In the Lurie et al. multicenter trial (82) conducted at five sites in the United States, France and Austria, there were more withdrawals in the surgical than the RFA treatment group. In the 48 patients randomized to the RFA arm, one patient was not offered treatment as they had previously undergone an intervention for their saphenous vein. In the surgical arm, four of the 40 patients randomized to that arm, did not undergo treatment. After randomization three patients excluded themselves from the trial and one failed to undergo surgery despite multiple scheduled appointments.

In the Subramonia et al. trial (88) conducted in the United Kingdom, 30 patients of the 128 assessed for suitability were excluded from randomization. The main reasons for exclusion included anatomical factors (n = 14) and pathophysiological factors (n = 14). Six other patients were listed as having other

reasons for exclusion. Of the 93 randomized patients, 48 were to the RFA arm and 45 were to the surgical arm. In the RFA arm, one patient did not undergo treatment whereas in the surgical arm, four patients did not undergo treatment. Of the four not undergoing surgery, two were for medical reasons (new onset hypertension, developed atrial fibrillation), one removed their name from the waiting list and one underwent treatment on the non-trial list.

In the Rautio et al. trial (85) conducted in Finland, 85 of the 121 patients screened, were excluded. The major reasons for exclusion included bilateral disease (n = 36), GSV diameter too large > 12 mm (n = 21), patients without GSV insufficiency or having simultaneous SSV reflux (n = 17), inappropriate candidates for day case surgery (n = 6) and patients refusals (n = 5). Of the 36 patient eligible for the trial, three refused due to unsuitable schedules and 33 were randomized, 16 were assigned to the RFA group, one patient excluded because of pregnancy and 17 to the surgery group, four patients refused due to a preference for the RFA treatment.

Patient preference for VV treatment was surveyed in a consecutive series of patients with symptomatic varicose veins referred to a vascular surgery service in the United Kingdom. (98) Of the 111 patients invited to complete the questionnaire, 83 (75%) completely answered and 28 (25%) partially completed the questionnaire. Although most patients (> 80%) were aware of surgical treatment for varicose veins they were less aware of endovascular treatments, only, 3% were aware of RFA and 11% were aware of ELT. Despite most patients (72%, 74/103) reporting not knowing enough about treatments to express a treatment preference, 23% (24/103) expressed a preference for endovenous treatment, either RFA, ELT or sclerotherapy. The majority (80%, 74/92) reported that their treatment decision would be influenced by the opinion of their surgeon.

Patients also reported a range of concerns for any treatment. Treatments that were to be performed in one session were strongly or moderately preferred by 76% (71/93) of the respondents. Discomfort after treatment was also a more important concern than time off work. Over half (58%, 54/93) of the respondents reported that time off work was not a concern. The employment status for these 54 respondents varied: 65% (n = 35) were not employed, 20% (n = 11) were employed full time and 15% (n = 8) were employed part-time. Recurrence after treatment was the issue that patients reported being the most concerned with.

Group B: Endovascular RFA versus Laser Ablation

Randomization Trials of Endovascular RFA versus ELT Ablation

Three RCT studies (90-92) compared RFA with endovascular laser ablation (ELT) for treatment of symptomatic varicose veins.

Two of the RCT studies (90;91) were conducted in the United States and one (92) was in the United Kingdom. The trials varied in the use of RFA catheter and laser devices. Treatment effectiveness was compared with the first generation RFA catheter (Catheter Plus) in one of the trials(91) and the second generation catheter (Catheter Fast) in two of the trials(90;92) and ELT was performed with different laser wavelengths, the 810-nm (91) and the 980-nm laser (90;92).

The Morrison et al. trial (91) was a within-person RCT that involved 50 patients with bilateral VV disease. The GSVs were randomly treated in one leg with RFA using the RFA ClosurePlus catheter while the other leg was treated with ELT (810-nm). The primary endpoint was ablation of the treated vein at 1 year follow-up, which occurred significantly more often ($p < .05$) in the RFA than the ELT treated veins at 80% (40/50) and 66% (33/50) respectively. The DVT rate in the author's overall institute experience was reported to be 0.8% and to be similar in the two treatment groups. The occurrences of paresthesia (< 1%), leg oedema (< 1%), and superficial thrombophlebitis (2.3%) were similar with the two treatments.

In the Almeida et al. trial (90), all procedures were performed by interventional radiologists in outpatient clinics (six sites) and with local tumescent anaesthesia. Sixty-nine patients were randomized and were not informed of their treatment assignments, which were either ELT with a 980-nm laser or RFA with the ClosureFast® RFA catheter. Primary endpoints for the study involved procedurally related complications, short term recovery and technical success at one month follow-up. Post-operative pain levels ($p < .0001$ at 2 weeks), tenderness ($p < .0005$ at 2 weeks) and ecchymosis or bruising ($p = .005$ at 1 month) were significantly less in the RFA group than the ELT group. Differences for pain and tenderness, however, were no longer significant at one month follow-up. Overall minor complications were less frequent ($p = .021$) among those treated with RFA (4.4%; 2/46) than with the laser (22%; 9/41). Complications in the ELT group included phlebitis (n = 6), erythema (n = 4) and paresthesia (n = 1), while in the RFA group, hyperpigmentation (n = 10) and paresthesia (n = 1) were reported. A DVT in a patient who underwent ELT was the only major adverse event to occur.

Although vein occlusion and elimination of treated vein reflux were not reported in the Almeida study, venous symptom improvement (VCSS) and quality of life scores (CIVIQ2) were evaluated at 2 weeks and at 1 month follow-up. At 2-weeks, the improvement in mean VCSS scores were significantly ($p = .0035$) higher in the RFA group (4.0 ± 1.8) than the ELT group (5.3 ± 1.9). At one month, symptom improvement was also higher (2.7 ± 2.2 versus 3.2 ± 1.8) but not significantly ($p = .2825$) in the RFA group. The improvement in global HRQOL scores were also significantly higher in the RFA group at 1 ($p = .006$) and 2-week ($p = .0034$) follow-up. At the 1-month follow-up, global HRQOL scores for the two treatment groups were not different (22.7 ± 50 versus 22.2 ± 3.3, $p = .6135$). The group differences in the global HRQOL scores were attributable mainly to differences in the pain and subsequent physical functioning sub scores in the global HRQOL measure.

In the Shepherd et al. study (92) interventions were performed at one center by one of three surgeon and were performed in the operating room under general anaesthesia with local tumescent anaesthesia. The trial objective was to compare the early outcomes following endovascular treatment with a 980-nm laser or RFA segmental ablation with the RFA Catheter Fast device. Patients randomly assigned to RFA (n = 67) or to ELT (n = 64) were not informed of their assignment. Two major complications were observed in the trial, one case of PE two weeks after RFA and one case of lymphatic leakage from the cannulation site in the ELT group. Three of the four patients requiring an overnight admission were treated by RFA. Minor complications were reported to be similar in the two groups and included infection (4.6%), wound hematoma (1.5%), thrombophlebitis (6.1%), saphenous vein paresthesia (9.9%) and skin staining (6.1%).

Post procedural pain scores were the primary outcome measures and unadjusted mean pain scores at 3 days ($p = .010$) and 10 days ($p = .001$) days were significantly better for RFA than for ELT. Pain scores remained significantly better for RFA than for ELT after an adjustment for differences in numerous factors (age, gender, body mass, symptom severity, disease pattern, vein ablated and number of phlebectomies). However, after adjustment for analgesic use, mean pain scores differences were no longer significantly different between the treatment groups.

Recovery evaluated as return to usual activity and to work after the procedure were similar between the treatment groups. The majority of the patients returned to normal activities within 3 days (ELT (50%, 25/50) and RFA (60%, 37/62). Differences between the groups were similar with recovery as the return to work within 3 days after the procedure was reported to be 37% after ELT and 41% after RFA. Secondary outcomes included measurements on venous clinical symptoms (VCSS scores) and HRQOL (AVVQ and SF-12) at 6 weeks. These outcomes were improved in both treatment groups and the between group differences for improvements for both vein symptoms (mean VCSS difference = -.01; $p = .777$) and HRQOL by the AVVQ[(mean difference = -0.3 p =.854) and the SF-12 (mean SF-12 global physical score difference =-2.6 p = .101) scores were not significantly different.

Comparative Cohort Series of Endovascular RFA versus ELT Ablation

Four controlled cohort studies (66;93;95;96) involved comparisons between endovascular RFA and ELT ablation for symptomatic varicose veins; all except one (96) were conducted in the United States. The Shepherd et al. study (96) which was conducted in the UK was the only study to employ the second generation RFA catheter and the more recent segmental approach to ablation.

In the Almeida et al. study (93) 819 ELT procedures (483 GSV) performed at one center by a vascular surgeon was compared to 128 RFA procedures (95 GSV) at another center. All endovascular ablation procedures were performed with tumescent anaesthesia. Four different laser wavelengths (810-nm, 940-nm, 980-nm and 1320-nm) were used for the ELT procedures. The RFA device was not identified. A life-table analysis was performed to evaluate treated vein ablation rates and at 500 days, primary closure rates were significantly higher ($p < .0001$) for ELT than for RFA (92% vs 85%) for RFA. Adverse events were reported to be minimal. Transient paresthesia developed in two legs in RFA group and two legs in the ELT group. Thrombus extension into the common femoral vein requiring anticoagulation occurred in two cases after ELT. The authors reported that since these early reports, protocols for both ELT and RFA have changed. In particular, for RFA there has been an increase in temperature from 85°C to 95°C and for ELT, an increase in energy delivery from 30-50 J/cm to 50 to 80 J/cm.

In the Marston et al. study (95) the study objective was to evaluate the treatment effectiveness of RFA and ELT for venous haemodynamic dysfunction represented in the more severe degrees of chronic venous insufficiency as defined by CEAP scores of 3 to 6. Endovenous saphenous vein ablation under tumescent anaesthesia was performed with the RFA ClosurePlus device in 58 legs (GSV < 12 mm) at one center and with an 810-nm laser in 31 legs (no diameter restrictions) at another center. Concomitant phlebectomy, if required, was performed with both treatments. Follow-up investigations at 3- 6 weeks included duplex ultrasound, vascular haemodynamics by air plethysmograph for vascular volume (VV), vascular filling index (VFI) and venous symptom improvement (VCSS scores).

At 6 weeks, complete ablation (to within 5 cm of SFJ) was obtained in 88% (51/58) of the RFA procedures and 84% (26/31) of the ELT procedures. Continuing flow in the GSV (> 10 cm from the SFJ) occurred in 5.9% (n = 3) of the RFA cases and 7.7% (n = 2) of the ELT cases. Reflux into the calf measured by the VFI was significantly improved over baseline in both treatment groups; 5.1 to 1.7 ($p < .005$) in the RFA group and 6.1 to 2.1 ($p < .01$) in the ELT group. Ninety-five percent of the limbs were improved after ablation yielding a normal VFI (< 2 mL/s) in 78% and a mildly abnormal VFI (2 - 4 mL/s in 17% of the cases. The post-operative VFI scores did not improve as greatly in the cases undergoing incomplete ablation compared to complete ablation. Venous symptoms significantly decreased in cases after complete ablation from 11.5 ± 4.5 at baseline to 4.4 ± 2.3 post-operatively. No significant differences between RFA and ELT ablation were reported. Two thrombotic events occurred, one involving a gastrocnemius vein thrombus in the RFA group and a partially occluding thrombus in the SFJ in the ELT group.

In the Puggioni et al. study (66) the objective was to compare early treatment efficacy including closure rates and complications between endovascular RFA and ELT treatment of symptomatic varicose veins performed at one site over two different consecutive time periods. RFA ablation (53 legs) with the ClosurePlus catheter (restricted to GSV diameters 2 to 12 mm) performed in the first 24-month study period was compared with ELT ablation (77 legs) with the 810-nm laser (without vein diameter restrictions) in the later period. Procedures were performed in the operating room under general or spinal anaesthesia with local tumescent anaesthesia. Concomitant phlebectomy, if required, was performed in both procedures.

The immediate technical success was 100% (77/77) for the ELT procedures and 96% (51/53) for the RFA procedures. RFA was also inadequately (significant persistent flow) performed intra-operatively necessitating a repeat procedure in nine cases whereas ELT was always successful (17% versus 0, p = .002). Early (within a month) postoperative ultrasound imaging was not part of the centers' protocol and was performed in 70% of the ELT and 21% of the RFA group after recognizing the implications of thrombus. Three asymptomatic cases of GSV thrombus protrusion in the CFV, all in the ELT group, were noted. Treatment included low molecular weight heparin in two cases, unfractionated intravenous heparin in one case and insertion of a temporary inferior vena cava filter in another case for a protrubent thrombis that appeared to be floating in CFV. In all cases the thrombus completely resolved at 12 or 95 day scans in short term follow-up. Overall minor complications were more common in the ELT group (16.6%; 13/77) than the RFA group (7.6% ; 4/53) and included urinary retention (ELT, n = 1), thrombophlebitis (ELT, n = 4), cellulitis (ELT, n = 2), haematoma (ELT, n = 1), oedema (ELT, n = 2; RFA, n=1) and excessive pain (ELT, n = 3; RFA, n = 3).

In the Shepherd et al. study (96) post-operative recovery including pain levels, analgesic use and return to work were compared in patients undergoing ELT (n = 35) with the 980-nm laser and RFA (n = 46) with the ClosureFast catheter device. The procedure performed was dictated by the availability of equipment and preference of the patient. All procedures were performed under general anaesthesia with tumescent anaesthesia with concomitant phlebectomies, if necessary, by experienced vascular surgeons (> 100 endovascular procedures).

Pain ratings using a 100-mm visual analogue scale were recorded in a 10-day pain diary. Pain scores and analgesic use was greatest in the first 3 post-operative days and median pain scores were higher, although not significantly (p = .053), in the ELT [25.8 mm (range, 0 to 80)] compared to the RFA [14.5 mm (range, 1 to 81) treatment group. At 10 days, median pain scores were significantly (p = .04) lower in the RFA group [13 mm (range, 0 to 68) than in the ELT [23.3 mm (range, 0 to 85)]. The return to normal activity was not significantly (p = .358) different between the two treatment groups; median 3 days (range, 0 to 11) for RFA versus median 5 days (range, 0 to 11) for ELT. The return to work duration, however, was significantly (p = .022) faster after RFA [median 5 days (range, 1 to 11)] than ELT [median 9 days (range, 1 to 11)].

GRADE Level of Evidence

The levels of evidence, as rated according to GRADE criteria (48), for the primary review research question on the comparative effectiveness of RFA with surgical ligation and stripping for varicose veins are outlined below in Tables 12A and 12B.

Table 12A: GRADE Level of Evidence for RFA versus Surgical Ligation and Stripping for Varicose Veins

Outcome	Study Design	Quality (Consort)	Consistency Effects	Directness and generalizability	Summary Study Findings	Overall Quality
Recovery	4 RCT	Moderate	Variable reporting but consistent outcomes	Appropriate range of patients (but with restrictions on target vein diameter for RFA) with recovery evaluated both as return to usual activity and return to work. Both procedures performed under general anaesthesia limiting comparison with RFA that does not require general anaesthesia	Even when general anaesthesia was used in both treatment groups, recovery as time to usual activity and to work was significantly faster after RFA than surgery on average a week less of lost work time.	Moderate
Vein occlusion or obliteration	5 RCT	Moderate	Results are generally comparable but sample sizes are small and focused mainly on post-operative period	Appropriate range of patients (but with restrictions on target vein diameter for RFA) with variably defined measures of ultrasound defined treatment success – vein closure, absence of flow, absence of reflux.	Intra-operative and post-operative occlusion rates were high and comparable with surgical stripping. Follow-up reports were limited and involved small numbers of subjects (followed for at most 3 years.)	Moderate
Vein Symptom Relief	3 RCT	Low to moderate	High degree consistency with , significant and comparable symptom improvements in both treatment groups	Appropriate range patients (but with restrictions on target vein diameter for RFA) with reliable and valid assessment indices	Significant improvement in vein symptoms reported in both groups with no between group differences but reports were generally only for the early post-operative period and actual mean scores often not reported..	Low to Moderate
HRQOL	4 RCT	Low	Improvements in QOL were consistently reported in all treatment arms but between group differences in QOL improvement were inconsistent – RFA comparable or better than surgery	Appropriate range patients (but with restrictions on target vein diameter for RFA) with reliable and valid assessment indices but timing of assessment in early post-operative period limits validity	Significant improvement in vein specific QOL in both groups with RFA having comparable or better improvements in QOL than surgery , but only one small trial reported on QOL beyond the immediate post-operative period.	Low
Recurrence	3 RCT	Low	Limited and variable reporting	Appropriate range of patients (but with restrictions on target vein diameter for RFA) with ultrasound defined varices reflux	Follow-up in the trials was limited mainly to post-operative period and the few trials reporting on 1, 2 or 3 year follow-up involved very small patient groups. There was some suggestion that neovascularization a significant predictor of long term recurrence occurred more commonly after surgery than RFA but trial groups were small.	Low
Patient satisfaction	3 RCT	Moderate	Limited and variable reporting	Appropriate range of patients (but with restrictions on target vein diameter for RFA)	Patient satisfaction was high in both treatment groups but generally higher with RFA than surgery in the post-operative period and at short term follow-up at 1 year.	Moderate

HRQOL; health related quality of life, RCT; randomized controlled trial

Table 12B: GRADE Level of Evidence for Endovascular RFA versus Laser Ablation for Varicose Veins

Outcome	Study Design	Quality (Consort)	Consistency Effects	Directness and generalizability	Summary Study Findings	Overall Quality
Pain and Recovery	2 RCT 1 CCT	High	Consistent reports	Appropriate range of patients, both interventions performed in outpatient setting with local anaesthesia and with recovery to both usual activity and return to work	Pain and bruising was significantly lower after RFA up to 2 weeks but not at one month or when pain was corrected for analgesic use. Recovery was comparable in the two groups.	Moderate
Vein occlusion or obliteration	1 RCT 3 CCT	Low	Inconsistent reporting and variable study designs	RCT involved cases of bilateral VV limiting generalizability and the CCT studies compared ablation techniques under vein restrictions applicable to RFA but not to ELT.	Ablation rates in the RCT and controlled clinical trials resulted in conflicting results	Low
Vein Symptom Relief	2 RCT	High	Consistent reports	Appropriate range patients with reliable and valid assessment but short term evaluation limits interpretation of treatment effectiveness	Vein symptom relief was significantly improved over baseline in both treatment groups but was higher after RFA than ELT at 2 weeks but not at I month.	Moderate
HRQOL	2 RCT	High	Consistent reports	Appropriate range patients with reliable and valid assessment but timing of assessment early post-operatively limits validity	Significant improvement in vein specific QOL were reported in both endovascular groups with no between group differences	Low
Recurrence	1 RCT 3 CCT	Low	Limited and variable reporting	RCT involved cases of bilateral VV limiting generalizability and the CCT studies compared ablation techniques under vein restrictions applicable to RFA but not to ELT.	Ablation rates in the controlled clinical trials resulted in conflicting results	Low
Patient satisfaction	NR	NR	NR	NR	NR	NR

HRQOL; health related quality of life, NR, not reported; RCT; randomized controlled trial

Discussion

Endovascular RFA treatment for symptomatic varicose veins has been available in North America and Europe since early 2000. This evidence review identified 11 cohort studies and 3 multicenter registry studies with over 3000 patients undergoing endovascular RFA ablation for VV. The RFA studies were mainly conducted in Europe and the procedures were usually performed by surgeons in operating theatres under conscious sedation.

Major adverse events after RFA ablation were uncommon and the overall major adverse event rate based on pooled events in RFA cohort studies was 2.9% (105/3,664). The most common adverse events were vascular events such as DVT with only one PE event being reported. Although saphenous nerve injury were infrequently reported, paresthesia usually confined to the thigh along the course of the treated vein were more commonly reported in studies. These events are more likely to be considered permanent nerve damage if persisting 6 months or beyond. Follow-up in the studies, however, rarely continued beyond 6 months and estimates of nerve damage are likely to be underestimated for both RFA and surgery. Studies examining the timing of these events also found that both paresthesia and skin burns tended to occur more often in the early case experiences and were more related to experience of the surgeons. A significant reduction was also reported in both events after the introduction of tumescent anaesthesia, which acts as a barrier for heat energy, to routine endovascular protocols.

Minor complications such as swelling, inflammation, hematoma and leg pain were relatively common after RFA, although it was not always certain to what extent these complications were attributable to the primary RFA treatment or concomitant procedures such as phlebectomy. Although the majority of patients undergoing endovascular ablation in these reports were in their forties and fifties, there was also a large cohort trial of elderly patients, which when compared to younger patients, demonstrated similar low complication rates, quick recovery and successful vein ablation and ulcer healing. This is particularly important because of the increasing prevalence of both VV and leg ulcers with increasing age.

Effectiveness and ablation rates

The RFA ablation system employed in all the trials was the Closure System® and the catheter device employed in the majority of the trials involved the first generation catheter which has been associated with technical limitations. The original FDA regulatory approval for this device was restricted to vein diameters < 12 mm and as such the majority of the trials evaluating RFA effectiveness were restricted to saphenous vein diameters usually < 12 mm. The cohort trials also all involved the great saphenous vein as the main target vein and no cohort trials evaluated RFA effectiveness of the small saphenous vein.

The technical success of RFA for saphenous vein ablation was evaluated with intra-operative and post-operative (usually within a month) imaging. Vein ablation in these studies was variably defined and reported to range from 60% to 90%. Failure to ablate veins intra-operatively can be corrected by repeating the process during the same procedure and several reports suggested that high repeat rates occurred. (66;76) The variable rates of RFA ablation in the short term were more likely the result of initial technical failures thought likely to be due to too rapid a catheter removal and/or inadequate use of compression techniques including tumescent anaesthesia.

Follow-up evaluation of treatment success within the first year were limited in the cohort studies and successful ablation at 6 month follow-up were in the high 80's although one cohort trial (71) reported successful occlusion of 95% . Only one cohort study (71) reported follow-up beyond 1 year and although complete disappearance of treated veins were reported in 90% (19/21) of the subjects followed at 2 years, the follow-up involved less than 20% (21/120) of the original study cohort.

The VNUS Closure Treatment study group a large prospective industry sponsored multicenter registry did

report on longer term follow up in several overlapping reports on registry subsets of patients. Successful ablation rates close to 90% were reported at one year follow-up and ablation rates in the mid 80% were also reported at subsequent annual follow-up points until 5 years. These rates, however, are difficult to interpret because of the limited follow-up of eligible patients from the recruited cohort at the various follow-up points. Even at 1 week only 81% of the eligible recruited sample were followed up and in later follow-up, the completion rate was 42% of the patients at 6 months and 13% of the patients at 3 years. This registry study is the only study group to report on longer term data up to 5 years. Their reports, however, involves follow-up for only a fraction of the original cohort limiting the estimate of treatment effectiveness. The overlapping reports on multiple patient subgroups over time, further complicates the evaluation of treatment effectiveness. Life table analysis was also not performed for this registry and would have given better estimates of treatment effectiveness.

RFA Second Generation Catheters and Segmental Ablation

The second generation RFA catheter device was designed to address some of the technical limitations with the first generation catheter such as the variable energy delivery and the lengthy procedure time. The main approach with the new catheter involves a segmental approach to energy delivery in that energy is constantly and uniformly delivered sequentially to overlapping 7 cm segments of vein. In comparison the former RFA catheter method involved a slow continuous catheter pull back and depending on the catheter speed could result in variable energy delivery down the vein. A higher temperature was also achieved with the new energy delivery method, up to 95^{o}C from 85^{o}C and continuous saline infusions were also no longer needed increasing the simplicity of the procedure. The procedure time was reported to be significantly quicker with these RFA modifications. In one report, the procedure time (catheter insertion to catheter removal) for a 37 ± 2 cm vein length was significantly decreased from 41 ± 5 minutes with the Catheter Plus to 16.4 ± 8.2 minutes with the Catheter Fast. (80)

However, at this time there were only two published cohort studies involving approximately 500 patients undergoing RFA ablation with the Catheter Fast device. (78;80) RFA treatments in these cohort studies were performed without saphenous vein diameter restrictions and were provided by surgeons in outpatient settings with tumescent anaesthesia. It was also of note that in this setting no major adverse events were reported in these studies. In these studies vein occlusion rates were also much higher than with the first generation catheter. Closure rates in the first year were close to 100% and were also reported to be as high for large (> 12 mm diameter) saphenous veins as for small (< 12 mm diameter) saphenous veins.

Comparative Effectiveness RFA versus Surgery

RFA ablation was compared to surgical ligation and vein stripping in five small RCT studies involving in total 142 patients undergoing RFA and 150 patients undergoing surgery. Patients in the trials were reported to be similar in the two treatment arms with respect to their age, gender, and disease stage. RFA treatment and surgery were not directly compared for patients with larger vessel disease as none of the trials employed the Catheter Fast catheter and large diameter GSV veins were exclusion criteria for the trials. The trials were also similar in that RFA procedures were performed by surgeons in operating rooms under general anaesthesia rather than in outpatient setting. Endovascular minimally invasive treatments such as RFA do not usually require general anaesthesia and can be adequately performed in outpatient settings with only local tumescent anaesthesia. Therefore the advantages of local anaesthesia, immediate ambulation, and the reduced risk of adverse events with RFA treatment were not fully evaluated in these studies. In addition only one trial employed tumescent anaesthesia, which is required not only to act as a heat barrier to the skin improving safety but also necessary to compress veins and ensure maximal contact with the heating element for effective ablation.

The main objectives of the trials were generally to evaluate technical success, procedural and post operative morbidity. Technical failures were reported for both the surgical and the RFA treatment groups.

For surgery, technical failures included duplex ultrasound documented incomplete stripping and were reported to occur in up to 15% of the cases. For RFA, technical failure was defined as ultrasound documented absent or partial vein occlusion and was reported to occur more variably in approximately 4% to 19% of the cases.

Procedural and post-operative complications occurred less often with RFA than the surgery group. As expected, infection events in the surgical groups related to surgical cut down for vein access were more common. Thermal skin injury was a complication only related to RFA and was generally avoided with tumescent anaesthesia. In general, however, the sample sizes in the trials were too small to develop reliable estimates of complication rates or detect treatment differences in complication events. A disadvantage for the RFA treatment was the significantly longer procedure time reported with the first generation RFA catheter. This may be less of a factor with the second generation RFA catheters and the segmental approach to vein ablation as procedure times with these changes were reported to be significantly faster. Despite performance of RFA in the operating room and use of general anaesthesia, patient recovery both to usual activity and to work, was significantly faster after RFA resulting in on average one week less time off work.

The secondary outcomes reported in the RCT studies were evaluated with clinical exams, duplex ultrasound imaging and validated outcome instruments for symptom relief and quality of life. Later imaging follow-up to three years showed low but inconsistent failure rates between treatment groups. The failure rates or patency rates in three different trials were higher in the RFA group at 1-year, similar at 2-years and not noted in either group at 3-years. Other measures of treatment success, vein symptom relief and HRQOL improvements were reported in several trials using validated measurement instruments. In all trials there were statistical improvements in vein symptoms in both treatment groups over baseline and between group differences were not significantly different. HRQOL outcomes although improved over baseline in both treatment groups, were evaluated mainly in the peri-operative period where improvements were more related to changes in symptoms than to actual impacts on broader measures of HRQOL. Nevertheless, in the one study evaluating impact on HRQOL at 2 years, improvements in HRQOL were reported to be higher for RFA treated patients.

The recurrence rate is a key measure of treatment success for both treatments. Recurrence rates after surgery have been reported to be extremely variable ranging from 20% to 80% depending on various patient, physician and technical factors. It has thus become a well known limitation of surgical ligation and vein stripping. (39;99;100) Neovascularization has been reported to be a major predictor of long term recurrence after surgery. (101-103) It has been suggested to be a natural response to injury related to the dissection and surgical ligation of the SFJ region and an inherent limitation to a surgical approach for venous reflux.(100). Neovascularization was also reported after RFA but less frequently. Comparisons between the treatment groups for recurrences in the RFA comparative studies identified in this review are limited due to the short follow-up period (three years at most) and the small patient groups followed (15 patients at 3 years). The VNUS Closure Treatment Study Group has been the only group to report on long term follow-up to 5 years follow-up but that follow-up was based only on a limited subset of the eligible recruited cohort. Longer term recurrence after RFA, at this time, is still undetermined.

Comparative Effectiveness Endovascular Ablation Techniques

Although the key comparator for RFA of venous reflux in the MAS review was surgery, other endovascular approaches including ELT and ultrasound guided foam sclerotherapy are also potential comparators to RFA. Sclerotherapy differs from the other two treatments in that vein closure is achieved through chemical ablation rather than thermal ablation and has been generally restricted to treatment for smaller diameter surface veins and for residual varices after surgery or ELT. (104;105) There have been no trials comparing RFA to sclerotherapy and only one trial compared sclerotherapy with ELT and that trial involved a patient choice design. (106) Vein closure in that trial was higher after ELT at early

follow-up and remained significantly higher at 1-year follow-up. The significance of vein diameter for successful vein ablation, however, was detailed for both sclerotherapy and ELT.

RFA, on the other hand, is based on similar principles of endovascular vein thermal ablation as ELT and both are possible treatment alternatives to surgery for venous reflux. In this evidence review, these endovascular treatments have been found to be compared in three RCT studies (90-92) with a small number of patients and in four controlled comparative trials. (66;93;95;96) Only one of the RCT studies (91) compared vein closure rates between the treatment groups and that was a within person randomization assignment for patients with bilateral disease. In that study ablation rate at one year was higher for RFA than ELT. The ablation rate, however, that were achieved with ELT was lower that generally reported in the literature and higher than that for RFA, particularly as the first generation catheter was used in the trial.

The other two trials, each using the ClosureFast catheter, compared the treatments with the primary outcome being post-operative pain. Ablation or vein closure rates were not reported in either trial. There is some evidence that in the immediate post operative period, there may be less patient discomfort and pain with the second generation RFA catheters than with ELT ablations. However, so far all of the comparative trials evaluated lasers of different wavelengths and power and all used bare or unshielded laser fibers. There is some evidence that ELT ablations performed with shielded laser fiber tips result in less trauma to vein wall resulting in less perforation, bruising and post-operative discomfort. (107;108) So far however, there have been no RCT studies comparing ELT ablations with various types of laser tips or comparing shielded laser fibers with RFA ablation.

Post-operative pain and symptom relief within 2 weeks were significantly better in the RFA treatment group but these differences were no longer significant at one month. The wide variation in pain reported by patients in both treatment groups was notable and in the one trial after correcting for analgesic use, pain differences between the treatment groups were no longer significant. Better pain management in both treatment arms are also likely to decrease pain levels for patients. The pattern of greater improvement in the RFA treatment group than the EFT group seen at 2 weeks but not at 1 month was also seen for symptom relief and quality of life. However as pain measures are included in both these outcomes, differences reported for these outcomes may be more likely related to the impact of differences in pain measures in this early post-operative period.

Most of the information on vein ablation comes from controlled clinical trials where differences in vein closure rates were compared within centers or between centers with different thermal ablation approaches at different follow-up periods. Only one of these trials (96) employed the second generation catheter (vein closure was not reported) and each of the studies employed lasers with different wavelengths. Ablation rates were reported to be similar between the treatment groups at 6 weeks and lower for RFA than ELT at 500 day follow-up. One of the studies focused only on technical success and intra-operative redo rates and reported a lower technical success and significantly higher redo rate with RFA ablation than ELT. (66) High redo rates for RFA ablation had also been reported in cohort studies. (76) In both these studies, the first generation catheter was employed rather than the second generation catheter with a segmental approach to ablation which were designed to improve on the technical ease, speed and effectiveness of the procedure.

Conclusion

Published cohort trials on endovascular RFA treatment of symptomatic VV generally involved ablation with first generation catheter prototypes and focused mainly on safety, recovery and technical success or short term effectiveness. The studies demonstrated a favourable safety profile for RFA ablation in that major adverse events were rarely reported and when reported were shown to be more related to early clinical experience. The variable short term vein ablation rates reported in the cohort studies were likely attributable to some extent to the technical limitations and intra-operative failures with the first generation catheter devices. Second generation RFA catheters employing a segmental approach to ablation were shown in cohort studies to result in shorter procedures times, fewer adverse events and higher ablation rates.

The RCT comparisons between surgery and endovascular RFA for primary venous reflux were with first generation RFA catheters and procedures were performed in operating rooms generally under general anaesthesia without tumescent anaesthesia. Although patient characteristics were similar for the study treatment groups, patients with large vessel disease were excluded because of RFA technical constraints. Study objectives involved a broad range of outcomes from several perspectives and in these comparisons patient outcomes were generally more favourable for RFA (results summarized in Table 13). Patients undergoing RFA exhibited less pain, lower minor complications and faster recovery than after surgery with at least one week less of work loss despite RFA procedures being performed in operating rooms under general anaesthesia.

Treatment effectiveness of RFA for VV was generally comparable with surgery. Technical failures occurred with both treatments but occurred more variably with RFA. Significant improvements in vein symptoms and HRQOL were reported in both treatment groups, but follow-up beyond 6 months was limited and involved small groups of patients limiting estimates of longer term treatment efficacy. Patient satisfaction, although high for both treatments, was higher for RFA than surgery.

There is limited evidence comparing endovascular techniques such as ELT and RFA for vein ablation. Randomized trial evidence suggests that in the post-operative period, RFA ablation with second generation catheter devices produces less pain and morbidity than ELT with uncovered laser fibers. Patient recovery after these ablative procedures, however, is similar. Comparative evidence on other treatment outcome measures is limited or absent. Although vein symptoms and HRQOL are significantly improved after both treatments they were evaluated only post-operatively and none of the studies reported comparisons of vein ablation rates.

Replacing surgery with endovascular ablation approaches such as RFA may offer system-related advantages as well as patient advantages. The treatment can be provided by several medical specialties and service delivery could be improved as image guided endovascular treatments do not require an operating room and could efficiently decant patients from the operating room to a more appropriate setting. This could also result in a related decrease in pre-operative works ups, demands on anaesthetists' time and hospital stay. Scheduling treatment as an outpatient procedure might also decrease the wait time and may be associated with more reliable scheduling.

Depending on the reimbursement mechanism for the treatment, however, insuring RFA may also result in closure of outpatient clinics with an increasing centralization of procedures in selected hospitals with large capital budgets resulting in larger waiting lists. A cost exercise suggests that the average case cost of RFA may be less than surgery, but the overall budget impact may be greater with insurance of RFA because of the transfer of the cases undergoing endovascular thermal ablation in the private market to the public payer system.

Table 13: Outcome Comparisons between RFA and Surgery and Between RFA and ELT for Varicose Veins

Outcome Comparators	RFA vs Surgery	RFA vs ELT
Post procedural pain, minor complications	RFA < Surgery	RFA < ELT
Recovery	RFA < Surgery	RFA ~ ELT
Major adverse events	RFA < Surgery	RFA ~ ELT
Effectiveness - Imaging vein occlusion/ absence	RFA ~ Surgery	RFA ? ELT
Effectiveness -Vein symptom improvement	RFA ~ Surgery	RFA ~ ELT
Effectiveness - Quality Of Life	RFA ~ Surgery	RFA ~ ELT
Recurrence	RFA ? Surgery	RFA ? ELT
Patient satisfaction	RFA > Surgery	RFA ? ELT
Patient preference	RFA > Surgery	RFA ? ELT
Procedure costs	RFA < Surgery	RFA ~ ELT
Budget impact	RFA < Surgery	RFA ~ ELT

ELT refers to endovascular laser ablation; RFA, radiofrequency ablation

Ontario Health System

Varicose veins are managed by various medical specialties including general practitioners, dermatologists, phlebologists (physicians who are vein specialists), surgeons (both general and vascular) and interventional radiologists (radiologists who provide image guided interventions). In Ontario, RFA is not an insured medical service for VV. In contrast, surgical ligation and stripping of saphenous veins is the standard treatment for symptomatic VV and an insured service. Phlebectomy, performed either as a co-intervention with surgery or as a stand-alone therapy in outpatient settings, is also an insured service. The wait time for these surgeries has been estimated to be over a year (Personal Communication, clinical experts, October 2009).

The volumes of surgeries and phlebectomies performed for VV treatment in Ontario over a 5-year period are listed Table 14. Surgical volumes were extracted from MOHLTC physician billing databases (codes R837, R844, R868, R869). The majority of the surgeries were for the more common cause of varicose vein reflux, the GSV. Repeat surgical procedures, ranging from 25% in 2002/2003 to 28% in 2007/2008, represented a significant proportion of the annual volumes. Overall, surgical volumes have been declining annually for a total decline of 28% over the past 6 years. The rate of repeat surgeries, however, has remained relatively constant.

The volumes of surgeries performed for the GSV, SSV and repeat procedures, are outlined in Table 15 by gender and by age. Women are more likely (67.6%) to undergo surgical treatment and exceed men by almost two-to-one in every age group. The peak demand for vein surgery occurs in the 45 to 54 year age range, but it remains high over the broader 35 to 60 year age range. The decline in volume after 65 years of age is inconsistent with the increasing prevalence of varices and leg ulcers with increasing age.

Table 14: Surgical Ligation and Saphenous Vein Stripping in Ontario from (2002 - 2008)

	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008
Great saphenous vein	3,467	3,228	3,046	3,029	2,766	2,403
Small saphenous vein	178	163	107	110	118	104
Repeat surgeries	1,197	1,081	997	1,163	1,045	974
Total Surgeries	4,842	4,472	4,150	4,302	3,929	3,481
Phlebectomy	3,643	3,156	3,074	3,157	2,785	2,623

Table 15: Combined Number of Claims for Surgical Ligation and Saphenous Vein Stripping (2007-2008)

Age Range	Female	Male	Total
15-24	22	18	40
25-34	290	108	398
35- 44	639	229	868
45-54	726	336	1,962
55-64	334	262	596
65-74	223	115	338
75-84	43	23	66
≥ 85	1	1	2
Total	**2,278**	**1,092**	**3,370**

Claims include GSV, SSV and repeat procedures

Economic Analysis

Study Question

The objective of this project was to assess the economic impact of endovascular radiofrequency ablation (RFA) for symptomatic varicose veins in the province of Ontario.

Economic Analysis Method

RFA and surgical vein stripping, the main comparator reimbursed by the public system, are comparable in clinical benefits. Hence a cost-analysis was conducted to identify the differences in resources and costs between both procedures and a budgetary impact analysis (BIA) was conducted to project costs over a 5-year period in the province of Ontario.

Economic Literature Review

A literature search was conducted on March 11th, 2010 and the following databases were searched:

- OVID MEDLINE
- MEDLINE In-Process and Other Non-Indexed Citations
- OVID EMBASE
- Wiley Cochrane
- CINAHL
- Centre for Reviews and Dissemination/International Agency for Health Technology Assessment
- EconLit

The search strategy is presented in Appendix 1B. We reviewed published articles that fit the following inclusion criteria:

- full economic evaluations [(cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimization analysis (CMA)]
- Economic evaluations reporting Incremental Cost-Effectiveness Ratios (ICER) i.e. cost per quality adjusted life year (QALY)/life years gained (LYG) or cost per event avoided or studies reporting total costs
- studies in patients with varicose veins
- studies reporting on RFA and vein stripping to manage varicose veins
- studies in English

Three articles were identified – two cost analyses and one CEA in a patient population with varicose veins.

Rautio et al. (85) compared RFA with conventional vein stripping in terms of short-term recovery and costs. Twenty eight patients with varicose veins were randomly assigned to RFA (n = 15) or surgical procedure (n = 13). Post-operative pain was assessed daily during the first week and on the 14th day. The length of sick leave was determined and health-related quality of life (HRQOL) was measured. Clinical outcomes were re-assessed 7-8 weeks after surgery with duplex ultrasonography. Direct medical costs and costs resulting from lost productivity were reported. The authors reported that all operations were successful and complication rates were similar between the groups. Post-operative average pain was significantly less severe in the RFA group than the stripping group. The sick leaves were significantly shorter in this group as well. The direct medical cost of RFA was estimated at $850 plus an estimated

annual investment cost of $3,360 versus $360 for conventional surgery. The authors concluded that RFA was cost-saving with the inclusion of the value of lost working days and that this procedure may offer advantages such as reduced post-operative pain, shorter sick leaves and faster return to normal activities versus conventional stripping.

Subramonia et al. (87) compared the costs involved in RFA and conventional surgery for lower limb varicose veins in a prospective randomized controlled trial (RCT). Patients were randomized to RFA or surgery. Direct medical costs and indirect cost to society due to sickness leave after surgery were calculated. Eighty eight patients (47 RFA and 41 surgery) were randomized. The authors reported that ablation was longer to perform and more expensive than surgery but enabled patients to return to work 1 week earlier than after surgery. The authors concluded that RFA cost is offset by a quicker return to work in the employed group.

Adi et al. conducted a CEA between RFA and vein stripping based on costs and quality of life measurements reported by Rautio et al.(49) It was assumed that the probability of survival was equivalent for RFA and stripping. The incremental cost per QALY of RFA compared to surgery was driven by differences in healthcare costs and utility (pain) gain. Utilities were imputed from the pain visual analogue scale (VAS) scores reported by Rautio et al. The authors concluded RFA to be a potentially attractive cost effective (i.e. incremental cost effectiveness ratio of £30,000 or less per QALY) alternative to conventional surgery for varicose veins. They further addressed the limitations of the analysis which was based on short-term data (2-week) and were therefore unable to address potential differences in long-term complications and recurrence rates and from a relatively poor quality RCT based on a number of assumptions, particularly the estimation of utility gain.

Target Population

The target population of this economic analysis was patients with symptomatic varicose veins.

Perspective

The primary analytic perspective was that of the Ministry of Health and Long-Term Care.

Resource Use and Costs

RFA is not currently being performed in Ontario. It has just been recently introduced into the Ontario market. Currently private clinics are performing endovascular laser treatment (ELT) and the public sector is performing vein stripping surgeries to treat varicose veins.

Private clinics are charging on average $2,950-$3,000 per leg to perform ELT (Personal Communication, Clinical expert, October 2009). Currently the average weighted cost absorbed by hospitals for the surgical vein stripping procedure coded as 1KR87(109) is approximately $1,059 per case. The code 1KR87 is defined as:

> Excision partial, veins of leg NEC (not else classified);
> includes: stripping and ligation, varicose veins of leg, stripping, varicose veins of lower limbs, that with hook avulsions;
> excludes: harvesting, lower limb vein (see 1KR58), sclerotherapy (see 1KR59);
> omit code: when performed with subfascial endoscopic perforator vein surgery (see 1KR51).

A weighted average cost was obtained by summing the products of the number of cases performed each year by the average direct cost of that year and then dividing it by the total number of cases for all years for the past six fiscal years. The direct costs and number of cases for this procedure was obtained from the Ontario Case Costing Initiative (OCCI). (110) OCCI provides an average cost per case derived from

hospitals in Ontario participating in the initiative. The data are limited because they are not capturing all the procedures performed in Ontario but it can provide an average estimate of the cost being absorbed by the hospital setting.

The following table describes the direct costs and number of cases associated with procedure 1KR87 within the hospital setting for the past six fiscal years (FY).

Table 16. Direct costs and number of vein stripping cases in the past six fiscal years in Ontario from Ontario Case Costing Initiative data set

Outpatient	# Cases	Average Direct Cost per Case	Std Dev	Min	Max
2002-2003	958	$1,438	$720	$198	$3,489
2003-2004	759	$911	$327	$129	$2,383
2004-2005	853	$869	$433	$62	$6,197
2005-2206	978	$1,133	$426	$6	$2,768
2006-2007	932	$796	$455	$83	$3,043
2007-2008	713	$1,077	$569	$112	$4,493
Weighted Averages:	**5193**	**$1,045**	**$492**	**$97**	**$3,694**

Inpatient	# Cases	Average Direct Cost per Case	Std Dev	Min	Max
2002-2003	33	$1,717	$962	$307	$5,111
2003-2004	12	$1,908	$1,367	$892	$5,883
2004-2005	18	$1,453	$514	$799	$3,140
2005-2006	6	$3,182	$4,402	$625	$12,098
2006-2007	13	$2,500	$1,500	$1,097	$7,117
2007-2008	FOI	FOI	FOI	FOI	FOI
Weighted Averages:	**82**	**$1,918**	**$1,260**	**$649**	**$5,621**

All Cases	# Cases	Average Direct Cost per Case	Std Dev	Min	Max
2002-2008	5275	$1,059	$504	$106	$3,724

OCCI data capture all direct costs associated with the procedure within the hospital context excluding fees associated with physician labour. Those fees are reported in the Ontario Schedule of Benefits (111) (OSB) under the following codes:

R868 – high ligation and stripping of long saphenous vein with groin dissection
R 869 – stripping of short saphenous vein with popliteal dissection
R837- multiple ligation and avulsion (phlebectomy)
R844 – recurrent varicose veins – multiple ligation and/or stripping

The following table describes the fees associated with each code and the assumptions made to cost out a cost for anaesthesia and surgical assistance since these tasks are costed on a per unit basis in the OSB.

Table 17. Physician codes being billed for vein stripping procedures in Ontario

Resource	Cost/unit	Assumption	Reference
Great saphenous vein surgery	$148.60		OSB R868
Anaesthesia	$119.16	assumed 2 hour surgery therefore 6 base	vascular surgeon in

		units plus 1 unit in the first hour and 2 units after the first hour up to and including the first 1.5 hours	Toronto; OSB R868
		assumed 2 hour surgery therefore 6 base units plus 1 unit in the first hour and 2 units	vascular surgeon in
Surgical assistance	$102.60	after the first hour	Toronto; OSB R868
Phlebectomy	$148.60	R837 is always performed with R868	OSB R837
		assumed 2 hour surgery therefore 6 base units plus 1 unit in the first hour and 2 units after the first hour up to and including the first	vascular surgeon in
Anaesthesia	$119.16	1.5 hours	Toronto; OSB R837
		assumed 2 hour surgery therefore 6 base units plus 1 unit in the first hour and 2 units	vascular surgeon in
Surgical assistance	$102.60	after the first hour	Toronto; OSB R837
Short saphenous vein surgery	$107.50		OSB R869
		assumed 2 hour surgery and adjust cost	vascular surgeon in
Anaesthesia	$119.16	based on proportion quoted above = $14.90	Toronto; OSB R869
		assumed 2 hour surgery and adjust cost	vascular surgeon in
Surgical assistance	$102.60	based on proportion quoted above = $12.83	Toronto; OSB R869
Recurrent vein surgery	$353.80		OSB R844
		assumed 2 hour surgery and adjust cost	vascular surgeon in
Anaesthesia	$119.16	based on proportion quoted above = $41.71	Toronto; OSB R844
		assumed 2 hour surgery and adjust cost	vascular surgeon in
Surgical assistance	$102.60	based on proportion quoted above = $35.91	Toronto; OSB R844

Vein stripping surgeries have been declining in the province by an average of 7% a year as reflected in Ontario billing data. The introduction of new technologies may be a plausible explanation for the decline in surgical procedures. The following table describes physician billings for vein stripping surgeries in the past six fiscal years obtained from a Ministry of Health and Long-Term Care (MOHLTC) database (112). These numbers were then used to project surgeries in a linear fashion based on previous years up to five years into the future described in Table 19.

Table 18. Number of physician billings for vein stripping procedures in the past six fiscal years in Ontario

Surgery	2002-2003	2003-2004	2004-2005	2005-2206	2006-2007	2007-2008
R868 (great saphenous vein strip)	3,467	3,228	3,046	3,029	2,766	2,403
R837 (phlebectomy)	3,643	3,156	3,074	3,157	2,785	2,623
R869 (short saphenous vein strip)	178	163	107	110	118	104
R844 (recurrent vein strip)	1,197	1,081	997	1,163	1,045	974
Total vein surgeries	4,842	4,472	4,150	4,302	3,929	3,481

Table 19. Vein stripping surgeries projected over five years in Ontario

Surgery	Year 1	Year 2	Year 3	Year 4	Year 5
R868 (great saphenous vein strip)	2,318	2,125	1,933	1,741	1,549

R837 (phlebectomy)	2,460	2,285	2,110	1,935	1,759
R869 (short saphenous vein strip)	80	65	51	37	22
R844 (recurrent vein strip)	970	940	910	880	850
Total Vein Surgeries	3,368	3,131	2,895	2,658	2,421

In order to calculate a procedural cost for RFA certain assumptions were made. It was assumed that the hospital cost and physician labour fees excluding anaesthesia and surgical assistance were the same as vein stripping surgery. The manufacturer also provided details on the generator with a capital cost of $27,500 and a lifespan of 5 years and the disposables (catheter, sheath, guidewire) with a cost of $673 per case (Personal Communication, Manufacturer, April 2010).

The following table describes the potential costs associated with RFA.

Table 20. Unit costs associated with vein stripping surgery and RFA

Resource	Unit	Vein Stripping	Radiofrequency Ablation	References
Hospital				
Procedure	per case	$1,059	$1,059	(110)
Medical Visits				
Great saphenous veins - surgeon	per case	$148.60	$148.60	(111)
Anaesthetist	per case	$119.16		(111)
Surgical assistant	per case	$102.60		(111)
Phlebectomy - surgeon	per case	$148.60	$148.60	(111)
Anaesthetist	per case	$119.16		(111) (2 components: vein stripping and phlebectomy)
Surgical assistant	per case	$102.60		(111) (2 components: vein stripping and phlebectomy)
TOTAL		**$1,799.79**	**$1,356.20**	
Equipment				
Generator	per machine		$27,500	manufacturer
Disposables	per case		$673	manufacturer

Vein stripping surgery data are available from physician billings since it is a publicly reimbursed procedure. RFA is not an insured service and data are not available and assumptions had to be made in order to calculate future projections.

According to clinical experts in the field, RFA will compete head to head with ELT for varicose veins and could therefore potentially capture a share of that market estimated at 25% per year in the first few years of introduction into the province. (Personal Communication, Expert opinion, April 2010) ELT has been introduced into the Ontario market first and therefore if publicly reimbursed would capture an already decreasing vein surgery market at estimates of 35% in the first year followed by 55% in subsequent years since clinicians have more experience with the technology (Personal Communication, Expert opinion, April 2010). Private data have also indicated that on average 70 ELT procedures were performed a month last year in the province of Ontario. Therefore on average it can be assumed that 840 procedures were performed last year. It was assumed that RFA would capture 25% of the ELT market when introduced.

The following table describes the projections and assumptions associated with the calculations.

Table 21. RFA ablation procedures projected over five years in Ontario

	Year 1	Year 2	Year 3	Year 4	Year 5	Assumptions	
Total number of ELTs in ON	840	924	1,016	1,118	1,230	assumed 70 procedures/mo in year 1 and a 10% increase every year	Private data from company that holds majority of the ELT market
Average VS surgery market capture by ELT	1,861	2,175	2,025	1,874	1,724	assumed ELT will capture VS market by 35% in the first year and then 55% in subsequent years	expert opinion
Total ELTs	2,701	3,099	3,041	2,992	2,954		
RFA capture of ELT market	675	775	760	748	738	assumed RFA would capture up to 25% of the ELT market	expert opinion
Leftover ELT after introduction of RFA	2,026	2,324	2,281	2,244	2,215		

ELT = endovenous laser treatment; VS = vein stripping; RFA = radiofrequency ablation

Ontario Perspective

The burden of vein stripping surgeries to the province was calculated by multiplying the number of cases for that year by the cost of the procedure which included the physician fee associated with that procedure and the hospital cost for the surgery. The following table describe the average burden to the province from vein stripping surgeries in previous years.

Table 22. Burden of vein stripping surgeries in Ontario from fiscal years 2002-2007

Procedure	2002-2003	2003-2004	2004-2005	2005-2206	2006-2007	2007-2008
Great saphenous vein stripping	5.0M	4.6M	4.4M	4.3M	4.0M	3.4M
Phlebectomy	1.3M	1.2M	1.1M	1.2M	1.0M	971K
Short vein stripping	247K	226K	149K	153K	164K	144K
Recurrent vein stripping	2.0M	1.8M	1.6M	1.9M	1.7M	1.6M
TOTAL	8.5M	7.8M	7.3M	7.6M	6.9M	6.1M

M = millions; K = thousands

Vein stripping surgeries can be expected to decline in future years in a linear fashion based on data from previous years. The following table represents the projected decline in burden.

Table 23. Burden of vein stripping surgeries in Ontario projected over five years without reimbursement for endovenous laser treatment

Procedure	Year 1	Year 2	Year 3	Year 4	Year 5
Great saphenous vein stripping	3.3M	3.0M	2.8M	2.5M	2.2M
Phlebectomy	911K	846K	781K	716K	652K
Short vein stripping	111K	91K	71K	51K	31K
Recurrent vein stripping	1.6M	1.5M	1.5M	1.4M	1.4M
TOTAL	5.9M	5.5M	5.1M	4.7M	4.3M

M = millions; K = thousands

RFA is expected to compete with ELT and may capture as much as 25% of its market. If ELT is reimbursed by the public sector then numbers will continue to increase from previous private data and share capture from the conventional surgical treatment market. Therefore, RFA cases will also increase since it will be capturing a share of the ELT market. These numbers are projected in the following table.

Market shares will of course depend on various factors, such as prevalence of disease, health systems capacity, patient preferences and physician willingness to perform the procedure given that this may not be as profitable under the public system. But simply looking at increase in numbers of procedures a year, it can be shown that the budget for this procedure will have an impact. In the basecase scenario we assumed that the hospital cost will remain the same for RFA as for vein stripping with a difference in physician billing because RFA, like ELT, does not require anaesthesia and surgical assistance.

The projected impact of all three technologies for varicose veins assuming all are reimbursed publicly is shown in the following table.

Table 24. Budget impact analysis of varicose vein technologies in Ontario – basecase scenario

BASECASE	Year 1	Year 2	Year 3	Year 4	Year 5
Vein Stripping Surgeries	2.74 M	1.75 M	1.59 M	1.44 M	1.29 M
Endovascular Laser Treatment	2.75 M	3.15 M	3.09 M	3.04 M	3.00 M
Radiofrequency Ablation	0.92 M	1.05 M	1.03 M	1.01 M	1.00 M

The Medical Services Advisory Committee (MSAC) in Australia issued a HTA report in March 2008 on ELT. (113) In that report it was assumed that the hospital cost of ELT was 60% that of vein stripping surgery. Since we assumed the RFA cost would be similar to ELT, we also varied the RFA hospital cost by 40% (cost per case = $627.08) in a one-way sensitivity analysis and projected the impact in Table 25.

Table 25. Budget impact analysis of varicose vein technologies in Ontario – sensitivity analysis scenario

Sensitivity Analysis	Year 1	Year 2	Year 3	Year 4	Year 5
Vein Stripping Surgeries	2.74 M	1.75 M	1.59 M	1.44 M	1.29 M
Endovascular Laser Treatment	1.89 M	2.17 M	2.13 M	2.09 M	2.07 M
Radiofrequency Ablation	0.63 M	0.72 M	0.71 M	0.70 M	0.69 M

Conclusion

RFA is comparable in clinical benefits to vein stripping surgery. It has the extra upfront cost of the generator and cost per case for disposables but does not require an operating theater, anaesthetist and surgical assistant fees. The impact to the province is expected to be 5M by Year 5 with the introduction of new ELT and RFA technologies and existing surgery for varicose veins.

Appendices

Appendix 1: Literature Search Strategies

Search date: March 9, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to February Week 4 2010>
Search Strategy:
---

1 exp Catheter Ablation/ (14056)
2 ((radiofrequency adj2 ablation) or RFA or radiofrequency obliteration).ti,ab. (7691)
3 1 or 2 (15637)
4 exp Varicose Veins/ (13087)
5 ((varicose adj2 vein*) or varices or varicosis).ti,ab. (14153)
6 exp Venous Insufficiency/ (4853)
7 ((venous or vein* or saphenous) adj2 (reflux or incomp* or insuff*)).ti,ab. (4410)
8 exp Saphenous Vein/ (11930)
9 saphenous vein*.ti,ab. (10152)
10 or/4-9 (39378)
11 3 and 10 (194)
12 limit 11 to (english language and humans) (169)

Database: EMBASE <1980 to 2010 Week 09>
Search Strategy:
---

1 exp radiofrequency ablation/ (6296)
2 ((radiofrequency adj2 ablation) or RFA or radiofrequency obliteration).ti,ab. (7446)
3 1 or 2 (10802)
4 exp varicosis/ (18536)
5 ((varicose adj2 vein*) or varices or varicosis).ti,ab. (10799)
6 exp vein insufficiency/ (4352)
7 ((venous or vein* or saphenous) adj2 (reflux or incomp* or insuff*)).ti,ab. (4243)
8 exp saphenous vein/ (5439)
9 saphenous vein*.ti,ab. (8670)
10 or/4-9 (32927)
11 3 and 10 (291)
12 limit 11 to (human and english language) (234)

Table A1: CINAHL literature search queries (publish dates: to March 2010)

#	Query	Results
S11	S3 AND S10	45
S10	(S4 or S5 or S6 or S7 or S8 or S9)	3011
S9	Saphenous Vein*	488
S8	(MH "Saphenous Vein")	341
S7	(venous or vein* or saphenous) and (reflux or incomp* or insuff*)	894
S6	(MH "Venous Insufficiency")	385
S5	varicose vein* or varices or varicosis	842
S4	(MH "Varicose Veins+")	1464
S3	S1 or S2	3770
S2	radiofrequency ablation or RFA or radiofrequency obliteration	907
S1	(MH "Catheter Ablation")	3527

Economics Literature Search Strategies

Search date: March 11, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, EconLit.

Database: Ovid MEDLINE(R) <1950 to March Week 1 2010>
Search Strategy:
---
1 exp Catheter Ablation/ (14098)
2 ((radiofrequency adj2 ablation) or RFA or radiofrequency obliteration).ti,ab. (7712)
3 1 or 2 (15682)
4 exp Varicose Veins/ (13103)
5 ((varicose adj2 vein*) or varices or varicosis).ti,ab. (14163)
6 exp Venous Insufficiency/ (4860)
7 ((venous or vein* or saphenous) adj2 (reflux or incomp* or insuff*)).ti,ab. (4415)
8 exp Saphenous Vein/ (11948)
9 saphenous vein*.ti,ab. (10168)
10 or/4-9 (39427)
11 3 and 10 (195)
12 exp Economics/ (415903)
13 exp Models, Economic/ (7000)
14 exp Resource Allocation/ (13083)
15 exp "Value of Life"/ or exp "Quality of Life"/ (84137)
16 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (184714)
17 ec.fs. (264409)
18 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (61730)
19 or/12-18 (705435)
20 11 and 19 (16)

Database: EMBASE <1980 to 2010 Week 09>
Search Strategy:
---
1 exp radiofrequency ablation/ (6296)
2 ((radiofrequency adj2 ablation) or RFA or radiofrequency obliteration).ti,ab. (7446)
3 1 or 2 (10802)
4 exp varicosis/ (18536)
5 ((varicose adj2 vein*) or varices or varicosis).ti,ab. (10799)
6 exp vein insufficiency/ (4352)
7 ((venous or vein* or saphenous) adj2 (reflux or incomp* or insuff*)).ti,ab. (4243)
8 exp saphenous vein/ (5439)
9 saphenous vein*.ti,ab. (8670)
10 or/4-9 (32927)
11 3 and 10 (291)
12 exp "Health Care Cost"/ (114724)

13 exp Health Economics/ (252459)
14 exp Resource Management/ (15539)
15 exp Economic Aspect/ or exp Economics/ or exp Quality Adjusted Life Year/ or exp Socioeconomics/ or exp Statistical Model/ or exp "Quality of Life"/ (530897)
16 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (115919)
17 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (57659)
18 or/12-17 (608282)
19 11 and 18 (56)
20 limit 19 to english language (49)

CINAHL

#	Query	Results
S18	S11 and S17	9
S17	S12 or S13 or S14 or S15 or S16	467227
S16	(cost* N1 benefit*) or costbenefit* or (cost N1 effective*) or costeffective* or econometric* or life value or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or sensitivity analys* or "value of life" or "willingness to pay"	18452
S15	(econom* or cost* or budget* or pharmacoeconomic* or pharmaco-economic* or valu*)	247316
S14	(MH "Quality of Life+")	29503
S13	MW ec	69563
S12	(MH "Economics+") or (MH "Resource Allocation+")	313066
S11	S3 AND S10	45
S10	(S4 or S5 or S6 or S7 or S8 or S9)	3011
S9	Saphenous Vein*	488
S8	(MH "Saphenous Vein")	341
S7	(venous or vein* or saphenous) and (reflux or incomp* or insuff*)	894
S6	(MH "Venous Insufficiency")	385
S5	varicose vein* or varices or varicosis	842
S4	(MH "Varicose Veins+")	1464
S3	S1 or S2	3770
S2	radiofrequency ablation or RFA or radiofrequency obliteration	907
S1	(MH "Catheter Ablation")	3527

Appendix 2: Additional Tables & Study Data

Table A1: Clinical Cohort Trials of RFA Ablation of the Great Saphenous Vein

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Boros 2008 Michigan, US	▪ 1 site ▪ 3 vascular surgeons ▪ Local tumescent anaesthesia with general anaesthesia	▪ To assess the need for high ligation of the SFJ and the subsequent risk of DVT	▪ 1 month	▪ Closure System, ClosurePlus catheter ▪ NR	▪ 219 p (73% F) ▪ Mean age 52, 53 ▪ 219 Legs ▪ RFA and ligation (n = 77), RFA only (n = 142)	SFJ ligation was by surgeon preference (one always, one never, one varied)
Dunn 2006 Nevada, US	▪ 5 sites ▪ Experienced operators (>200 procedures) ▪ Local tumescent anaesthesia with intravenous or oral sedation	▪ To determine complication rates relief of pre-operative symptoms and saphenous vein occlusion rates	▪ 3 days 6 months	▪ Closure System ▪ 90^{O}C, 5-6 cm pullback ▪	▪ 68 p (85% F) ▪ Mean age 551 years (range 23 – 83) ▪ 85 Legs ▪ GSV < 12 mm	Concomitant phlebectomy and sclerotherapy performed
Goldman 2002 California, US	▪ 1 site ▪ Dermatologist ▪ Tumescent anaesthesia	▪ To evaluate initial experience with RFA saphenous veins	▪ 6 months	▪ Closure System ▪ 85^{0}C, ▪ 3.5 cm/sec average pullback rate	▪ 47 p (74% F) ▪ 50 Legs ▪	Concomitant phlebectomy
Hingorani 2004 Florida, US	▪ 1 site ▪ Vascular surgeon ▪ General anaesthesia (44%), regional femoral block (45%), local anaesthetic with sedation (11%) with local tumescent anaesthesia	▪ To evaluate closure rates and incidence of post-operative DVT	▪ 1 month	▪ Closure System ▪ 85 ^{O}C ,, 2-3 cm pullback	▪ 66 p (73% F) ▪ 73 Legs	Concomitant phlebectomy and subfascial endoscopic perforator ligation when indicated

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Manfrini 2000 Italy, Sweden, US, UK	▪ 16 private clinics and university centers in Europe ▪ Vascular surgeons ▪ ▪ General anaesthesia (20%), conduction anaesthesia (50%), local tumescent anaesthesia (30%)	▪ To assess clinical outcomes of two different RFA catheters	▪ 6 months, ▪ 12 months	▪ Closure catheters (5F, 8Fr), for veins 2 – 12 mm and Restore catheters (8Fr, 9Fr) for veins 4 – 15 mm) ▪ Closure at 85%C with 2.5 to 3.0 cm/min pull back and Restore catheter at 72)C with pull back rate guided by wall impedance	▪ 210 p (73% F) ▪ 151 Legs ▪ 152 veins ▪ Mean age 45 (SD 13 years)	▪ Concomitant high ligation of SFJ in 40%.
Puggioni 2009 New York, US	▪ To evaluate the safety of RFA in patients with prior venous thrombotic events ▪ 3 vascular surgeons ▪ General or spinal anaesthesia in first 12 months (43%) and local tumescent anaesthesia in the last 16 months (57%)	▪ To evaluate the safety of RFA in patients with prior venous thrombotic events	▪ 1 month	▪ Closure System ▪ 85^{o}C with pull back rate 2 cm/min in first 15 months (30%) and 90^{0}C with pullback rate 2-3 cm/min (70%) for remainder	▪ 274 p (68% F) ▪ 293 Legs ▪ Mean age 60 years (SD 15 years) ▪ No vein diameter exclusion	▪ No concomitant procedures with tumescent anaesthesia
Salles-Cunha 2004 Ohio, US	▪ 1 site ▪ 3 vascular surgeons ▪ Regional or general anaesthesia with local tumescent anaesthesia	▪ To evaluate the effectiveness of RFA ablation of saphenous veins	▪ 8 months	▪ Closure System ▪ 85^{O}C with mean pullback rate 3 cm/min	▪ 84 p (82% F) ▪ Mean age 54 (SD 13 years) ▪ 100 Legs	▪ Concomitant SFJ ligation and microphlebectomy (91%)
Salles-Cunha 2004 Ohio, US	▪ 1 site ▪ 3 vascular surgeons ▪ Regional or general anaesthesia with local tumescent anaesthesia	▪ To evaluate the development of small vessel networks at the SFJ and in the thigh	▪ 9 months (range 4 – 25 months)	▪ Closure System ▪ 85^{O}C with mean pullback rate 3 cm/min	▪ 89 p (82% F) ▪ Mean age 54 (SD 13) range 25 - 83 ▪ 106 Legs	▪ Concomitant SFJ ligation (93 legs ligated) and phlebectomy

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Tzillinis 2005 Ohio, US	▪ 1 site ▪ Vascular surgeons ▪ Regional or general anaesthesia with local tumescent anaesthesia	▪ To evaluate RFA operative morbidity in older compared to younger cohort	▪ Post operative clinical assessment	▪ Closure System ▪ 85^{O}C with mean pullback rate 2-3 cm/min	▪ 421 p ▪ Group 1 ≥ 70 years [35 p (41 legs) mean age 75 ± 4 years ▪ Group 2 < 70 years [386 p (449 Legs) mean age 47 ± 11 years	▪ Concomitant SFJ ligation and phlebectomy
Vasquez 2007 New York, US	▪ 1 site ▪ Vascular surgeon ▪ Tumescent anaesthesia and intravenous sedation	▪ To identify risk factors associated with RFA treatment failures using venous symptom severity scores	▪ 4 months	▪ Closure System ▪ 85^{O}C with 2-3 cm/min pullback rate ▪	▪ 499 p (68% F) ▪ Mean age 53.5 ± 13.3 years ▪ 682 Legs	▪ No concomitant adjunctive procedures were performed
Weiss 2002 Maryland, US	▪ 1 site ▪ Vascular surgeons ▪ Tumescent anaesthesia and intravenous sedation	▪ To evaluate the effectiveness of RFA in long term follow-up	▪ 2 years	▪ Closure System ▪ 85^{O}C ± 3 ^{O}C with mean pullback rate 2-3 cm/min	▪ 120 p (74.5% F) ▪ Age NR ▪ 140 Legs	Concomitant phlebectomy (62%) No high ligation was performed
Welch, 2006 Maryland,US	▪ 1 site ▪ Vascular surgeon ▪ General anaesthesia (n = 3) and local, tumescent anaesthesia with intravenous sedation (n = 181)	▪ To evaluate the efficacy of RFA alone for symptomatic varicose veins	▪ 9 months	▪ Closure System ▪ 85^{O}C to 90^{O}C with 2-3 cm/sec pullback rate	▪ 146 p (76% F) ▪ Mean age 48.4 (range 22 – 78) ▪ 184 Legs	Staged phlebectomy or sclerotherapy
VNUS Closure Treatment Study Group						

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Merchant – Closure Group 2002	▪ 30 registry sites in United States, Europe and Australia ▪ Vascular surgeons ▪ General anaesthesia at some sites, most sites used local anaesthesia (tumescent or regional or both) with or without sedation	▪ To evaluate 2-year efficacy outcomes after RFA in multicenter international industry sponsored prospective registry	▪ 2 years	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 286 p (74% F) ▪ Mean age 46.7 years (range, 19 to 78 years) ▪ 318 Legs	▪ Concomitant procedures included phlebectomy (58.6%) and sclerotherapy (3.5%). No high ligation of the SFJ was done
Nicolini – Closure Group 2005	▪ 23 registry sites ▪ Vascular surgeons ▪ General anaesthesia usually performed, local anaesthesia (regional or tumescent) was used at some sites	▪ To evaluate 3-year efficacy outcomes after RFA in multicenter international industry sponsored prospective registry	▪ 3 years (68 legs from 8 centers ▪ 2 years (148 legs from 17 centers) ▪ 1 year (252 legs from 23 centers)	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 294 p (76.9% F) ▪ Mean age 46.3 years (range, 18 – 97 years) ▪ 330 Legs	▪ Phlebectomy either concurrent or in follow-up performed in 61% ▪ No high ligation was performed
Merchant – Closure Group 2005	▪ 12 registry sites ▪ Vascular surgeons ▪ Tumescent anaesthesia with 45.5% of cases	▪ To evaluate 4-year efficacy outcomes after RFA in multicenter international industry sponsored prospective registry	▪ 4 Years (98 evaluated of 696 legs) ▪ 3 Years (114 evaluated of 886 Legs) ▪ 2 Years (210 evaluated of 1,026 Legs) ▪ 1 Year (384 evaluated of 1,077 Legs)	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 890 p (78.1% F) ▪ Mean age 47.6 years (range, 15 - 97) ▪ 1078 Legs ▪ (GSV only, included, 58 veins > 12 mm diameter))	▪ Concomitant procedures included phlebectomy or sclerotherapy. No high ligation was performed

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Merchant – Closure Group 2005	▪ 32 registry sites ▪ Vascular surgeons ▪ General anaesthesia usually performed, local anaesthesia (regional or tumescent) was used at some sites	▪ To evaluate 5-year efficacy outcomes after RFA in multicenter international industry sponsored prospective registry	▪ 5 years (117 evaluated of 406 legs) ▪ 4 Years (119 evaluated of 833 legs) ▪ 3 years (133 evaluated of 991 legs) ▪ 2 Years (263 evaluated of 1,141 legs) ▪ 1 year (473 evaluated of 1,206 legs)	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 1006 p (78.1% F) ▪ Average age 47.4 years (range, 15 to 97 years) ▪ 1,222 Legs ▪ All veins not treated with high ligation were included	▪ Concomitant procedures included phlebectomy or sclerotherapy. No high ligation was performed
Chandler- Closure Group 2000	▪ 27 registry sites ▪ Vascular surgeons ▪ General anaesthesia usually performed, local anaesthesia (regional or tumescent) was used at some sites	▪ To compare efficacy of RFA with and without SFJ ligation	▪ 1 year	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 166 p (77.1% F) ▪ Age range 19 to 78 years ▪ 60 legs high ligation, 106 legs without high ligation	▪ Concomitant phlebectomy with high ligation (60%) and without high ligation (79%)
Pichot – Closure Group 2004	▪ 5 registry sites in Austria, France and the United States ▪ Vascular surgeons ▪ General anaesthesia usually performed, local anaesthesia (regional or tumescent) was used at some sites	▪ To assess clinical and duplex ultrasound findings for patency and neovascularization in the groin and thigh 2 years after GSV RFA	▪ 2 years	▪ Closure System ▪ 85^{O}C with pullback rate 3 cm / min	▪ 56 p (73% F) ▪ Median age 50 years (range, 27 to 74 years) ▪ 63 Legs (No high ligation was performed)	▪ Concomitant phlebectomy (50 Legs) and staged phlebectomy or sclerotherapy (20 legs)
Closure System with ClosureFast Catheter Clinical Study Group						

Author, Year, Country	Sites, Operators, Anaesthesia	Objective	Follow-Up	Radiofrequency System, Temperature, Pull back Rate	Sample (% Female)	Concomitant or Staged Procedures
Calcagno 2009 Pennsylvania, US	▪ 1 site ▪ 2 operators ▪ Local tumescent anaesthesia	▪ To evaluate efficacy of the new generation ClosureFast RFA catheter larger (> 12mm diameter) veins	▪ 6 months	▪ Closure System – ClosureFast catheter ▪ 120^{O}C	▪ 310 p (F NR) ▪ 342 GSV and SSV 246 veins ≤ 12mm (mean diameter 8 mm ± 3 mm), 96 veins > 12 mm (mean diameter 17 mm ± 4 mm)	▪ NR
Proebstle 2008 Germany, France	▪ 8 sites in Germany, and France ▪ Vascular surgeons ▪ Local tumescent anaesthesia	▪ To evaluate the feasibility, safety and early clinical outcomes of RF-powered segmental thermal obliteration (RSTO)	▪ 6 months	▪ Closure System – ClosureFast catheter ▪ 120^{O}C with 20 second durations	▪ 194 p (73.8% F) ▪ Mean age 50.5 ± 13.6 years (range, 18 to 80) ▪ 252 Legs	▪ Concomitant phlebectomy (71.4%) and foam sclerotherapy for (13.9%) for tributary veins
Creton 2010 Germany, France	▪ 8 sites in Germany and France ▪ Vascular surgeons ▪ Local tumescent anaesthesia	▪ To evaluate the 1 year clinical outcomes of RSTO	▪ 1 year	▪ Closure System – ClosureFast catheter ▪ 120^{O}C with 20 second durations	▪ 225 p (73.8% F) ▪ Mean age 50.6 ± 13.6 years (range: 18 to 80) ▪ 295 Legs	▪ Concomitant phlebectomy (56.6%) and foam sclerotherapy for (12.9%) for tributary veins

Table A2: Complications and Adverse Events Following RFA Ablation of the Great Saphenous Vein

Author, Year, Country	Patients (p) Legs (L) Veins (V)	Follow-Up	RFA Device	DVT	PE	Phlebitis	Hematoma	Skin Burns or Necrosis	Paresthesia Dysesthesia	Nerve Injury	Infection
Boros 2008 Michigan, US	219 p 219 Legs (77 with SFJ ligation,142 no ligation)	1 month	Closure System with ClosurePlus catheter	4% (in ligation and without ligation)	0	-	-	-	-	-	5%
Dunn 2006 Nevada, US	68 p 85 Legs	6 months	Closure System with ClosurePlus catheter	0	0		2% (2/83)	0	3 days 1%(1/83) 6 months 4% (3/73)		
Goldman 2002 California, US	47 p 50 Legs	6 months	Closure System with ClosurePlus catheter	0	0	0	0	0	0	0	0
Hingorani 2004 Florida, US	66 p 73 Legs	1 month	Closure System with ClosurePlus catheter	16% (12/73)	0	-	-	-	-	-	-
Puggioni 2009 New York, US	274 p 293 Legs	1 month	Closure System with ClosurePlus catheter	Acute thrombotic event 13% (38/293legs – thrombus protrusion in to the SFJ (24, 8%), CFV (2.5%) and calf vein thrombus (7,2.5%)	0			0		0	0
Salles-Cunha 2004 Ohio, US	84 p 100 Legs	8 months	Closure System with ClosurePlus catheter	NR							
Salles-Cunha 2004 Ohio, US	89 p 106 Legs	9 months	Closure System with ClosurePlus	NR							

Author, Year, Country	Patients (p) Legs (L) Veins (V)	Follow-Up	RFA Device	DVT	PE	Phlebitis	Hematoma	Skin Burns or Necrosis	Paresthesia Dysesthesia	Nerve Injury	Infection
			catheter								
Tzillinis 2005 Ohio, US	421 p (35 ≥ 70 years, 386 > 70 years) 490 Legs	1 month	Closure System with ClosurePlus catheter No cardiac, respiratory or renal complication and no hospitalizations								
Vasquez 2007 New York, US	499 p 682 Legs	6 months	Closure System with ClosurePlus catheter	0.2% (1/633) non occlusive asymptomatic resolving after warfarin trherapy (patient was on long term warfarin after prior PE).		Thrombophlebitis 12% (76/633 L)		0	0.3% (2/633)		0.5% (3/633)
Weiss 2002 Maryland, US	120 p 140 Legs	6 months	Closure System with ClosurePlus catheter					0	Paresthesia 10% (12/120) all in the first year prior to tumescent anaesthesia, all except 1 resolved within 6 months	1 paresthesia not resolved within 6 months	
Welch, 2006 Maryland,US	146 p 184 Legs	9 months	Closure System with ClosurePlus catheter	0	0	Superficial thrombophlebitis, in 4.3% (8/184)		0	Numbness in 20.1% (38/184) 4 not resolved within one month	0	0
Endovenous Reflux Management Study Group											

Author, Year, Country	Patients (p) Legs (L) Veins (V)	Follow-Up	RFA Device	DVT	PE	Phlebitis	Hematoma	Skin Burns or Necrosis	Paresthesia Dysesthesia	Nerve Injury	Infection
Manfrini 2000 Italy, Sweden, US, UK	210 p 151 Legs	12 months	Closure System with ClosurePlus catheter and Restore catheter	Closure catheter: - Thrombus CFV 3.5% (3/86) Restore catheter- 16%(11/68) occlusive thrombus		3% (2/68) symptomatic phlebitis		3 burns with full thickness	Closure- 9% (9/104) to thigh and just below knee 49% (21/43) below knee. At 6 months,13 of 16 followed still had paresthesia\ Restore catheter – paresthesia 3% (2/68)	At 1 year, of the 5 followed, 3 had persistent saphenous or sural nerve paresthesia	
VNUS Closure Treatment Study Group											
Merchant – Closure Group 2002	286 p 319 Legs sites Dec 98 – June 2000	2 years	Closure System with ClosurePlus catheter	See 4 yr report	See 4 year F-Up report	See 4 year F-Up report		4.2% (6/143) in ear;y cases and O/143 in later cases			
Nicolini – Closure Group 2005	294 p 330 L 23 sites Dec 98 – Nov 99	3 years	Closure System with ClosurePlus catheter								
Merchant – Closure Group 2005	890 p 1078 Legs 12 centers 4 year data	4 years	Closure System with ClosurePlus catheter	0.5% (4/858) localized thrombus formation at SFJ that did not extend more than 10% into CFV	0.1% (1/858)	3.3% (28/858) at week 1 0.2% (1/446) at 6 months		1.7% (first 484 treatments 0.5% after tumescent anaesthesia	Paresthesia (focal hypoplasia) 12.1% (104/858) 1 week Pre-tumescent 14.5% (70/484) and 9.1% (34/374) post tumescent 6.7% 6 months, 2/.0% at 4 years		0.2% vein access site
Merchant – Closure Group 2005	1006 p (1,222 L) 12 centers 5 year data	5 years	Closure System with ClosurePlus catheter						12.3% (121/985) at 1 week 7.3% at 6 months 2.6% at 5 years		

Author, Year, Country	Patients (p) Legs (L) Veins (V)	Follow-Up	RFA Device	DVT	PE	Phlebitis	Hematoma	Skin Burns or Necrosis	Paresthesia Dysesthesia	Nerve Injury	Infection
Chandler-Closure Group 2000	60 legs RFA and high ligation, 120 legs RFA only	1 year	Closure System with ClosurePlus catheter	Femoral vein thrombus propagation in RFA only 0.8% (1/120)				3% (2/60) in RFA and ligation 3% (4/120) in RFA only	25% (15/60) in RFA and high ligation 16% (19/120) in RFA only		
Pichot – Closure Group 2004	5 registry sites 56 p 63 Legs	2 years	Closure System with ClosurePlus catheter	Safety not reported							
Calcagno 2009	310 p 342 Legs	6 months	Closure System with ClosureFast catheter	0	0	Superficial thrombophlebitis 4% (15/3420		0	Numbness 1% (3/310) at 2 weeks		
Proebstle 2008	194 p 252 Legs 8 sites in Germany and France	6 months	Closure System with ClosureFast Catheter	0	0	0.8% (2/252) Thrombophlebitis as pain and reddening along course treated GSV Hyperpigmentation in course phlebitis 2% (5/252)	Hematoma at puncture site .6% (4/252) – See Creton 1-yr f_Up	0	Paresthesia in localized patches in 3.2% (8/252)	0	0
Creton 2010	225 p 295 Legs 8 sites in Germany and France	1 year	Closure System with ClosureFast Catheter	0	0	Superficial thrombosis 1% Hyperpigmentation in 3.1%	Hematoma at puncture site 1.4% (4/295)	0	Parathesia 3.4%	0	0

Table A3: Study Quality of RFA Ablation Controlled Clinical Trials

Author, Year	Study Design	Randomize	Allocation Concealment Blinding	Inclusion Exclusion Criteria Stated	Intention to Treat Analysis	Power Calculation	Baseline Characteristics	Attrition Reported Loss to Follow-Up		Overall Study Quality
								RFA	Surgery	
Radiofrequency Ablation Versus Surgery										
Hinchliffe et al, 2006	2-arm within-person RCT	Randomization method not stated	No/not clear	Yes	Yes	Yes	Similar	0/16	0/16	moderate
Kianifard et al, 2006	Matched case control	Not randomized	No	No	Yes	No	Similar	0/51	0/51	low
Lurie et al, 2003, 2005	2-arm RCT	Web based random assignment	No/not clear	Yes	Yes	No	Similar	2/45	6/40	high
Stotter et al, 2006	3-arm RCT	Randomization method not stated	No/not clear	Yes	Yes	No	Similar	1/20,	1/20,1/20	moderate
Subramonia et al, 2008, 2010	2-arm RCT	Web based random assignment with age/sex stratification	No/not clear	Yes	Yes	Yes	Similar	0/47	0/41	high
Rautio et al, 2002 Perala et al, 2005	2-arm RCT	Sealed envelopes	No/not clear	Yes	Yes	No	Similar	0/15	0/13	moderate
Radiofrequency Ablation versus Endovascular Laser Ablation										
Almeida et al, 2009	2-arm multi-center RCT	Web based random assignment	Yes	Yes	Yes	Yes	Similar	0/46 (RFA)	0/41 (ELT.)	moderate
Morrison et al, 2005	2-arm within-person RCT	Randomization method not stated	No/not clear	No	Yes	No	Not Reported	0/50 (RFA)	0/50 (ELT.)	low
Shepherd et al. 21010	2-arm RCT	Internet based randomization service	Yes	Yes	Yes	Yes	Similar	1/67 (RFA)	3/64 (ELT)	high
Almeida et al, 2006	CCT	Contemporary comparison groups	No/not clear	No	No	No	Similar	128 (RFA)	819 (ELT)	low

Author, Year	Study Design	Randomize	Allocation Concealment Blinding	Inclusion Exclusion Criteria Stated	Intention to Treat Analysis	Power Calculation	Baseline Characteristics	Attrition Reported Loss to Follow-Up		Overall Study Quality
								RFA	Surgery	
Marston, at al,, 2006	CCT	Contemporary comparison groups –inter center	No	Yes	No	No	Similar	58 (RFA)	31 (ELT)	low
Puggioni at al,, 2005	CCT	Contemporary comparison groups – RFA in first 24-month study period followed by ELT for next period	No	Yes	No	No	Different; Vein diameter all sizes ELT vs 2 – 12 mm vein diameter range in RFA	53 (RFA)	77 (ELT)	low
Shepherd et al, 2010	CCT	Contemporary comparison groups	No	Yes	No	No	Similar	46 (S-RFA)	35 (ELT)	low

CCT; Controlled clinical trials, S-RFA sequential radiofrequency ablation

Table A4: Study Outcomes and Endpoints Reported in Clinical Trials Involving RFA

Author, Intervention Arms	Primary Outcome	Secondary Outcomes	Other Outcomes
Radiofrequency Ablation vs. Surgical Ligation and Vein Stripping			
Hinchliffe et al, 2006 RFA versus	▪ Reflux in treated vein segment at 3 months ▪ Vein disease specific QOL (AVVSS) at 3 months, 1 year	▪ Postoperative complications and pain ▪ Time to return to work/usual activities ▪ Cosmesis at 3 months ▪ Patient satisfaction at 3 months	▪ ND
Kianifard et al, 2006 RFA + surgical ligation GSV versus surgical ligation GSV and stripping	▪ ND	▪ ND	▪ Post operative pain- 30 days ▪ Bruising – 30 days ▪ Cosmesis – 30 days ▪ Satisfaction – 60 days ▪ GSV recanalization
Lurie et al, 2003, 2005 ELT versus surgical ligation GSV and cryostripping	▪ Recurrent vein incompetence on duplex imaging at 6,12,24 months ▪ Venous clinical severity score (VCSS) at 6,12 and 24 months ▪ Venous disease specific QOL (AVVSS) at 6, 12 and 24 months	▪ ND	▪ Procedure duration ▪ Post procedural complications ▪ Time to return to usual activities ▪ Postoperative pain and in duration
Stotter et al, 2006 RFA versus	▪ Clinical effectiveness [QALY (SF – 6D)] at 2 years ▪ Direct and indirect costs ▪ ICER	▪ ND	▪ ND
Subramonia et al, 2008, 2010 RFA and surgical ligation GSV versus surgical ligation GSV and stripping	▪ Haematoma at 1 week ▪ Venous disease specific QOL (CIVIQ) at 4 weeks	▪ Post operative pain and analgesic use ▪ Time to work recovery ▪ Cosmetic result 4 months ▪ Patient satisfaction at 4 months ▪ Complications (paresthesia)	▪ ND

Author, Intervention Arms	Primary Outcome	Secondary Outcomes	Other Outcomes
Rautio et al, 2002 Perala et al, 2005 RFA versus surgical ligation GSV and perforate invagination stripping	▪ Closed or absent GSV at 6 months	▪ Technical results and post procedural complications ▪ Post operative pain ▪ Return to work/normal activities ▪ Venous clinical severity score (VVSS) ▪ Venous specific QOL (AVVSS) ▪ Generic QOL (SF-36) ▪ Direct and indirect costs	▪ Adverse events
Radiofrequency Ablation Versus Endovascular Laser Treatment			
Almeida et al, 2009	▪ Post operative pain ▪ Ecchymosis ▪ Adverse procedural sequelae (deep vein thrombosis, paresthesia, phlebitis, hyperpigmentation and infection)	▪ Vein occlusion and elimination truncal reflux at 48 hours, 1 month ▪ Venous disease severity (VCSS)at 48 hrs, 1 week, 2 weeks, 1 month ▪ Limb tenderness at 48 hrs, 1 week, 2 weeks, 1 month ▪ Postoperative pain and analgesic use ▪ Vein disease specific QOL (CIVIQ)	▪ ND
Morrison et al, 2005	▪ Vessel ablation with no flow on color doppler in any portion of the treated vessel at 1 year ▪ Recurrent patency in any portion at 1 year	▪ ND	▪ ND
Shepherd et al. 2010	▪ Pain and analgesic use post-operatively at 3, 10 days	▪ Vein symptoms (VCSS) at 1 week and 6 weeks ▪ Disease stage (CEAP) ▪ Venous specific QOL (AVVSS) ▪ Return to work/normal activities ▪ Complications at 1, 6 weeks	▪ ND
Almeida et al, 2006	▪ Vein closure rate in follow-up to 500 days ▪ Recanalization rate in follow-up to 500 days	▪ ND	▪ Adverse events
Marston, at al, 2006	▪ Venous haemodynamic dysfunction (CEAP)	▪ Venous reflux ▪ Venous dysfunction (venous volume,, venous filling index ▪ Vein ablation	▪ ND

Author, Intervention Arms	Primary Outcome	Secondary Outcomes	Other Outcomes
Puggioni at al,, 2005	▪ Early efficacy and side effects	▪ ND	▪
Shepherd et al, 2010	▪ Evaluate postoperative pain and identify predictors	▪ ND	▪

ND; not done

Table A5: Clinical Trials Involving RFA Ablation versus Surgical Treatment for Varicose Veins

Study	Trial Design Objective	Subjects	Co-Interventions	Setting Operator Anaesthesia	Follow-Up
Hinchliffe, 2006 (81)	2-arm within-person RCT Operative and post-operative pain and morbidity in recurrent bilateral VV	75% (12/16) F Median age 54 years (range 44 – 66)	Concurrent, phlebectomy	Operating theatre Surgeon General anaesthesia	6 weeks
Kianifard , 2006 (89)	Matched case control Occurrence of angiogenesis at 1-year	39% (20/51) F Mean age 5.4 range 28-83	NR	NR Vascular surgeon	1 week 1 year
Lurie 2003, 2005 (82;83)	2-arm RCT Intra-operative and early (4-mo) post-operative complications, recovery, HRQOL Vein ablation, symptoms and HRQOL at 1 and 2-yrs	73% (52/80) F Median age RFA = 49 ± 4 years, surgery = 47 ± 4	Concurrent , adjunctive procedures limited to below knee	Operating theatre 5 sites, surgeons Tumescent anaesthesia with or without regional or general anaesthesia	4 months 2 years
Rautio 2002 (85) Perala , 2005 (84)	2-arm RCT and costing Post-operative pain, sick leave, HRQOL,, costs	93% (26/28) F Mean age RFA = 33 ± 6.7 years, surgery = 38 ± 6.8 years	Concurrent, phlebectomy	Operating theatre Surgeon and for RFA surgeon and an interventional radiologist General anaesthesia	8 weeks 3 years
Stotter 2006 (86)	3-arm RCT Post-operative morbidity, pain, vein closure Recanalization and neovascularisation at 1-yr	72% (43/60) F RFA = men 41 years , women,44 years Invagination stripping = men 54 years, women 51 years Cryostripping = men 42 years, women 41 years	Adjunctive procedures not performed	Operating theatre surgeon General anaesthesia	6 weeks 1 year
Subramonia 2008, 2010 (87;88)	2-arm RCT Vein symptoms, vein ablation and costs	69% (61/88) F Median age RFA = 47years (range 38-58), surgery = 45 years (range 37 – 53)	Concurrent, phlebectomy	Operating theatre Surgeons General anaesthesia	1 week 5 weeks

* RCT refers to randomized controlled trial; GSV, great saphenous vein; SFJ, saphenofemoral junction

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