Endovenous laser therapy (ELT) for varicose veins

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and costeffectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Mr Ben Hoggan and Dr Alun Cameron from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) and Dr Stephen Goodall from the Centre for Health Economics Research Evaluation (CHERE). The report was edited by ASERNIP-S.

This recommendation was endorsed by the Minister for Health and Ageing on 20 May 2008.

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The procedure

Endovenous laser therapy (ELT) is a minimally invasive treatment of varicose veins. It is performed in an outpatient setting using local anaesthesia or light sedation, primarily for patients with ultrasound-documented great or small saphenous vein reflux. The procedure involves introduction of a laser probe into the lumen of the saphenous vein, followed by the application of laser energy which occludes the vein. The fibre and catheter are slowly withdrawn, occluding the length of the vein and abolishing venous reflux.

The most appropriate comparator for ELT is surgical saphenous junction ligation and vein stripping. Ligation involves tying off the great or small saphenous veins at the saphenopopliteal or saphenofemoral junctions respectively. Stripping involves insertion of a stripper into the saphenous vein; the vein is then attached to the end of the stripper, which is gently withdrawn, and the vein is removed through the point of exit. Ligation and stripping are commonly performed together for great saphenous reflux whereas ligation alone is more frequently chosen for small saphenous reflux. The operation is usually performed under general anaesthesia.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures- Surgical (ASERNIP-S) in South Australia was engaged to conduct a systematic review of the literature on endovenous laser therapy for varicose veins. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of endovenous laser therapy (ELT) for varicose veins

Clinical need

While the previous MSAC review of ELT found no studies describing the prevalence of varicose veins in the Australian population, prevalence rates for varicose veins were reported in the general community of countries with similar ethnic composition to Australia, ranging from 6.8 to 39.7 per cent in men and from 24.6 to 39.0 per cent in women (MSAC 2003).

Data from the Medicare Benefits Schedule (MBS) indicates that in Australia it is predominantly women who seek treatment for varicose veins, and that demand for

treatment appears to peak between 35 and 64 years of age for both men and women. Statistics from the Australian Institute of Health and Welfare (AIHW) state that in the year 2004-2005, there were 16,272 public and private hospital admissions for the treatment of varicose veins in lower extremities. In the same time period, 14,950 procedures were performed for the interruption of saphenofemoral and/or saphenopopliteal junction varicose veins using the current 'gold standard' of surgical saphenous junction ligation and vein stripping.

Varicose veins may recur after treatment. Statistics from the MBS show that while 8,335 junction ligation and vein stripping procedures of the saphenous veins were performed during 2006-2007, 2,036 ligation and stripping procedures for the re-treatment of varicose veins were performed within the same period. This need for recurring treatment may place a considerable burden on health services.

Varicose veins are relatively common. However, it is their degree of severity that is likely to influence the demand for health services. Although the prevalence of milder forms of varicose veins is high, this may not necessarily translate to clinical burden. Clearer definitions of varicose veins that reflect degrees of severity are needed to determine prevalence rates and more accurately assess the clinical burden on the community.

Safety

A total of 57 studies were included in this review for the assessment of the relative safety of ELT and surgical junction ligation with or without vein stripping. This included five comparative studies that allowed a direct comparison of the safety of the two procedures. Three of the five comparative studies reported safety outcomes and adverse events clearly and stratified by treatment group. Few significant differences in morbidities and adverse events, either major or minor, were found between ELT and surgery. However, the differences that were found generally favoured the ELT procedure; ELT was found to have lower occurrence rates of haematoma, bruising, oedema and post-procedural pain.

All case series assessed in this review reported on at least one safety outcome or adverse event related to ELT or ligation and stripping. Self-limiting minor morbidities such as ecchymosis and bruising, induration, a sensation of tightness in the limb and post-operative pain were common adverse events associated with ELT. In the majority of cases these symptoms were self-limiting or only required treatment with mild medications. More serious complications, such as pulmonary emboli, deep venous thrombosis and nerve damage were uncommon. Pulmonary embolism was reported in only one patient who experienced no long-term consequences. Twenty cases of deep venous thrombosis (0.4 per cent of reported limbs) were identified across all patients treated with ELT; the majority resolved spontaneously without further treatment. Seventeen cases of nerve injury (0.8 per cent of reported limbs) were reported after ELT; the after-effects of two cases of neuritis persisted from 4 to 8 months, one case of sural nerve palsy resolved after 6 months, while one case of saphenous nerve damage had not resolved after 12 months.

Morbidities such as ecchymosis and bruising, paraesthesia, haematoma and post-procedural pain were common adverse events associated with surgical ligation and stripping. While these events are usually self-limiting, paraesthesia can persist over an extended period of time, while haematoma on occasion requires surgical drainage for resolution. Among the more serious complications, 30 cases of deep venous thrombosis

(1.5 per cent of reported limbs) and 23 nerve injuries (2.4 per cent of reported limbs) were reported after ligation and stripping; rates of resolution were generally not reported for either morbidity.

The ELT procedure in some cases led to minor adverse events not reported after ligation and stripping, such as laser skin burn and induration, and ELT appeared to have a slightly higher incidence of some other minor adverse events. However, the literature indicated that more serious complications such as deep venous thrombosis, nerve injury and paraesthesia, post-operative infection and haematoma were more common after ligation and stripping than after ELT.

From the available literature it appears that the ELT procedure is at least as safe as the comparative procedure of conventional surgical junction ligation with or without vein stripping.

Effectiveness

A total of five studies that directly compared ELT with surgical ligation and stripping were available to assess the relative effectiveness of the two procedures. Two of these studies were randomised controlled trials (Level II evidence); the remaining three were non-randomised experimental trials (Level III evidence) that either treated patients with ELT and surgical vein stripping across different time points or did not report the method of patient allocation. Comparisons regarding the clinical outcome of abolition of reflux were not possible for the majority of studies, as clinical outcomes of surgical vein stripping were reported poorly or not at all. This was further compounded by the different means of reporting the outcome of ELT and vein stripping with respect to reflux.

Among the comparative studies, reflux was absent in 94.1 to 95.5 per cent of limbs treated with ELT at the conclusion of follow-up. The study with the longest follow-up (12 months) reported 95.5 per cent of limbs treated with ELT remained free of blood flow or reflux. After ligation and stripping of the great saphenous vein, reflux was absent in 94.4 to 100.0 per cent of limbs at the conclusion of follow-up. The study with the longest follow-up (12 months) reported 94.4 per cent of limbs remained free of blood flow or reflux. No significant differences in rates of reflux abolition were reported between ELT and ligation and stripping. It appears that ELT is an effective treatment for occluding the saphenous vein, and is at least as effective as the conventional surgical operation.

A number of differences were found between ELT and ligation and stripping with respect to non-clinical effectiveness outcomes. ELT patients reported fewer symptoms of varicose veins and better scores on a number of quality of life domains than ligation and stripping patients; however, many of these differences were statistically significant for only a short period of time after treatment. ELT patients were also reported to require less time to return to work than patients who had undergone ligation and stripping, and mean operating time for ELT was found to be significantly shorter than for conventional surgery.

From the literature available ELT appears to be potentially more effective in the short term, and at least as effective overall, as the comparative procedure of saphenous junction ligation and vein stripping for the treatment of varicose veins.

Cost-effectiveness

The cost-effectiveness analysis was derived from the clinical effectiveness data previously described. This showed ELT to be at least as effective as the comparator, with potentially reduced short-term postoperative pain and faster resumption of normal activities.

A cost-analysis was conducted based on the assumption of no significant differences between treatments in primary clinical outcomes. Based on a number of estimates and assumptions, receiving ELT rather that surgical vein stripping for the treatment of unilateral varicose veins is associated with a modest cost saving (estimated incremental cost per patient = -$171), despite ELT being associated with the higher procedural fee, capital cost of the ELT equipment, duplex ultrasound, additional sclerotherapy and disposable laser fibre and catheters. These costs are offset by reduced staffing costs and a saving in the cost of day surgery, as opposed to hospitalisation.

The potential impact of ELT on the Australian healthcare system was also examined; clinical opinion suggests a short-term increase in demand for varicose vein treatment after the addition of ELT to the MBS, up to a maximum of 50 per cent above current levels in the first year (estimated additional cost to the healthcare system of $18,868,000), decreasing to 10 per cent above current levels in the third year and stabilising after that period.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of endovenous laser therapy for varicose veins compared with saphenous junction ligation with or without vein stripping.

MSAC finds that endovenous laser therapy is at least as safe, effective and cost-effective as saphenous junction ligation and vein stripping for the treatment of varicose veins.

MSAC recommends that public funding is supported for endovenous laser therapy.

The Minister for Health and Ageing accepted this recommendation on 20 May 2008.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of endovenous laser therapy (ELT), which is a therapeutic technology for varicose veins. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including input from clinical experts.

In November 2003, MSAC reviewed the evidence associated with ELT for the treatment of varicose veins (MSAC 2003). Based on the lack of evidence pertaining to effectiveness and cost-effectiveness at that time, MSAC recommended that public funding should not be supported for the procedure at that time. The current review was sought as a result of additional evidence for the ELT procedure becoming available since the previous report.

Readers are advised that the MSAC recommendation herein is dependent on both the results presented in the current assessment report and those of the previous MSAC report assessing the safety and effectiveness of ELT (MSAC 2003). The MSAC (2003) report can be accessed via: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1059-1/$FILE/msac1059.pdf

The MSAC terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

An advisory panel with expertise in vascular surgery, radiology, general practice, health economics and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. Membership of the advisory panel is provided at Appendix B.

This report summarises the assessment of current evidence for ELT for the treatment of varicose veins.

Background

Endovenous laser therapy for varicose veins

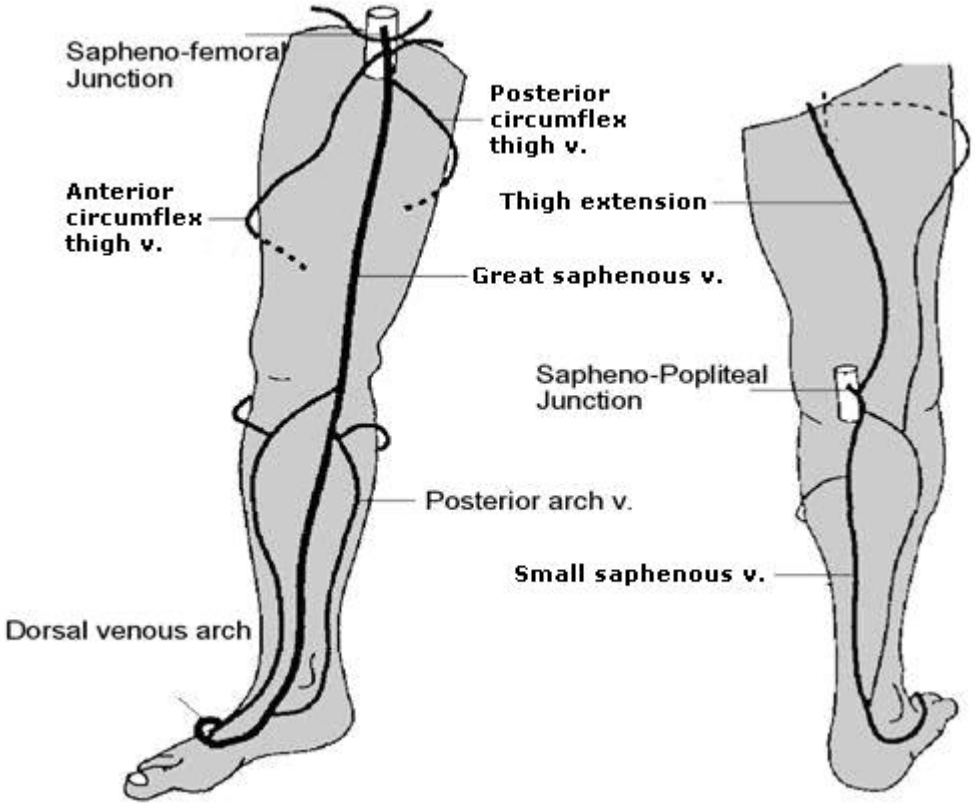
Varicose veins

The great saphenous vein (GSV), also referred to as the long saphenous vein, begins along the inner arch of the foot and ascends deep to the superficial fascia along the inner side of the leg, through the thigh to the femoral vein. The small saphenous vein (SSV), also called the short or lesser saphenous vein, begins at the outer arch and ascends along the Achilles' tendon to the popliteal vein (Gabella 1995) (Figure 1). Blood returning to the heart from the legs must work against gravity. Muscle contractions in the lower legs, aided by elastic vein walls, pump blood back to the heart, and one-way valves in the veins close to prevent back flow.

Chronic venous disease (CVD) may affect the great or small saphenous veins and/or tributaries. Varicose veins, a common form of CVD, are characteristically tortuous and dilated superficial tributaries protruding above the skin surface. It is now considered that the primary abnormalities in varicose veins are a loss of structural strength in the vein wall, damage to valves along the length of affected veins, or both (Fan 2003; Golledge & Quigley 2003). Disease generally starts in the mid-portion of saphenous veins or their tributaries, and blood flows both up and refluxes down under gravity due to inadequate valve function. At a later stage, dilatation extends to the saphenofemoral or saphenopopliteal junctions, rendering them incompetent and allowing free reflux from the heart level down through the great or small saphenous veins or their tributaries, a condition known as venous reflux. This markedly worsens disease, increasing the size of veins and worsening symptoms, with the potential for complications due to damage to skin and fat in the legs. Varicose veins can, however, occur without significant incompetency of the valves at the saphenous junction (Harrison 2001; Lofgren 1985).

The exact cause of varicose veins is unknown. Several risk factors that exacerbate the condition have been identified, including increasing age, gender, family history, obesity and pregnancy (Callam 1994). Frequently reported symptoms include localised swelling, heaviness, cramp and aches, chronic localised fatigue, itching and tingling. One or more of these symptoms and the presence of clinically demonstrated reflux are indications for intervention (Bradbury et al 1999). More serious symptoms, eg thrombophlebitis, bleeding, venous dermatitis and skin pigmentation as a prelude to venous ulceration, also require intervention (Wolf & Brittenden 2001). Symptoms may be exacerbated by prolonged periods of standing or sitting (Bradbury et al 1999; Lofgren 1985; Tisi & Beverley 2003). Varicose veins should be differentiated from superficial telangiectases, commonly referred to as spider or thread veins, and reticular veins (NICE 2000).

Figure 1 Great and small saphenous veins



Source: modified from Cuzzilla 2007, used with permission

CVD is commonly graded using the CEAP (clinical, (a)etiologic, anatomic, pathophysiologic) classification, endorsed by the American Venous Forum, the Joint Council of the Society for Vascular Surgery and the North American-International Society for Cardiovascular Surgery (Porter & Moneta 1995). Limbs with chronic venous disease are classified according to clinical signs (C), (a)etiology/cause (E), anatomic distribution (A), and pathophysiologic condition (P). Through this classification system CVD can be clinically scored, ranging in severity from C0 to C6. Clinical signs for each score are shown in Table 1.

Table 1 CEAP classification

CEAP classification	Clinical signs
C0	No visible or palpable signs of venous disease
C1	Telangiectases or reticular veins
C2	Varicose veins; distinguished from reticular veins by a diameter of 3mm or more
C3	(O)edema
C4	Changes in skin and subcutaneous tissue secondary to CVD, divided into two subclasses to better define differing severity of venous disease:
	C4a: Pigmentation or eczema
	C4b: Lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

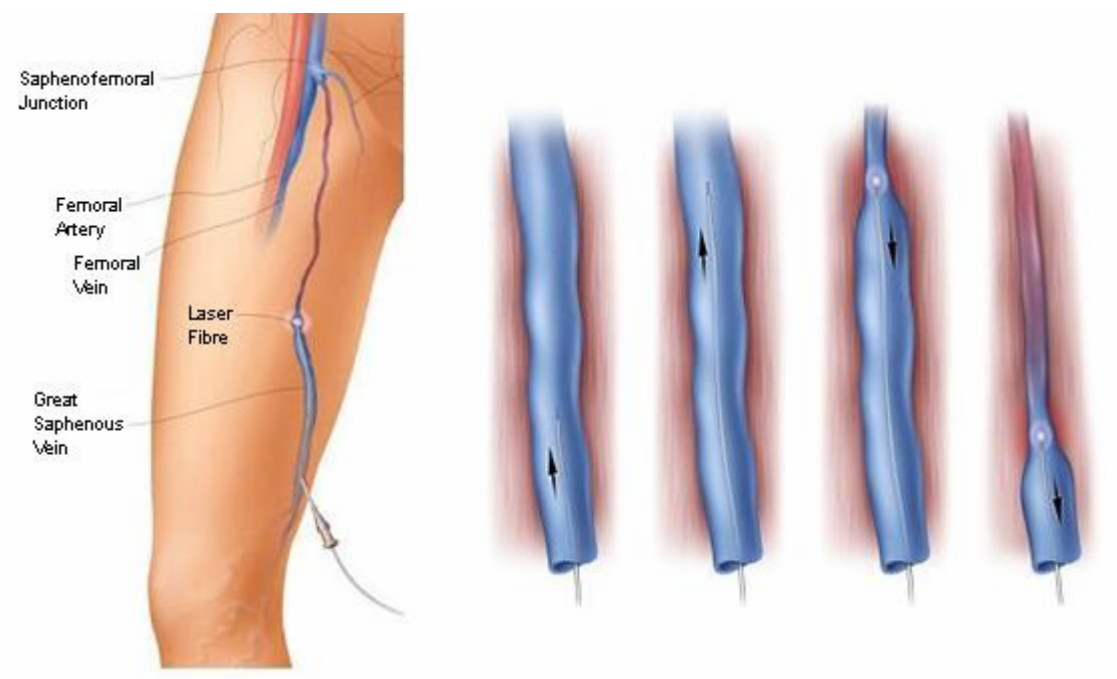
CEAP: Clinical, etiology, anatomy, pathophysiology; CVD: Chronic venous disease
Source: Eklof et al 2004

Endovenous laser therapy

Endovenous laser therapy (ELT) was introduced for the minimally invasive treatment of varicose veins in approximately 2000-2001. It is performed in an outpatient setting using local anaesthesia or light sedation, primarily for patients with ultrasound-documented great or small saphenous vein reflux.

After ultrasound examination to confirm the site and extent of saphenous reflux, a catheter is introduced into the vein along a guide wire via percutaneous puncture at the distal extent of the diseased saphenous vein. Perivascular infiltration of dilute local anaesthetic along the length of the vein is then performed under ultrasound guidance to collapse the lumen and compress the vein onto the catheter, to dissipate heat generated during the procedure so as to prevent tissue damage, and to anaesthetise the vein. The guide wire is replaced with a laser probe introduced through the catheter to just below the saphenofemoral or saphenopopliteal junction, with positioning confirmed by ultrasound. Laser energy is then applied as the fibre and catheter are slowly withdrawn so as to close the vein and abolish venous reflux (Figure 2). The delivery of laser energy directly to the vein wall produces endothelial and vein wall damage, occluding the vein and leading to subsequent fibrosis; ultrasound shows that the vein gradually shrivels and disappears by about 12-18 months on average. Upon completion of the procedure, the puncture site is dressed and graduated compression stockings and/or bandages are applied, and the patient is instructed to walk immediately (Diomed Ltd 2001; Min et al 2001; Myers et al 2006; Navarro et al 2001).

Figure 2 Endovenous laser therapy of varicose veins, insertion of laser fibre and withdrawal, showing vein ablation



Source: Diomed Ltd 2001, used with permission

A range of laser wavelengths can be used to achieve occlusion. The presumed target for lasers with 810, 940, and 980 nm wavelengths is intravascular red blood cell (haemoglobin) absorption of laser energy (Weiss & Munavalli 2005). It is possible that this produces steam bubbles as blood is boiled within the lumen and that these cause vein wall damage (Proebstle et al 2002). A 1064 nm laser that also targets haemoglobin

has been used, although this laser is not available in Australia. It is possible that this wavelength may cause a relatively high number of adverse effects, as shown in a clinical study by Chang and Chua (2002). An alternative to these wavelengths that is gaining acceptance is a 1320 nm wavelength that is claimed to target and heat water (as opposed to haemoglobin) in the bloodstream (Weiss & Munavalli 2005), although this has yet to be confirmed in vivo. However, there is also evidence to suggest that all laser wavelengths may work through the same mechanism, that is, by direct thermal ablation of the inner vein wall (Mordon et al 2007).

Caution should be exercised when comparing different lasers, as there is no strong evidence to indicate that any particular wavelength is superior to any other.

Intended purpose

Endovenous laser therapy for varicose veins is indicated for patients with clinically documented primary venous reflux, confirmed by duplex ultrasound, of the great or small saphenous veins. These patients have exhausted other conservative treatment measures and sclerotherapy is considered unlikely to be successful.

There are absolute and relative contraindications in patients

- who are pregnant (absolute)
- with occlusive deep vein thrombosis (absolute)
- who are unable to ambulate (relative)
- with known hypercoagulability (relative)
- with occlusive arterial disease (relative)
- with tortuous veins (relative).

Clinical need / burden of disease

Chronic venous disease (CVD) includes a spectrum of disorders, from asymptomatic varicose veins to chronic leg ulcers, and has been described as 'one of the most common conditions affecting humankind' (Callam 1994). While the previous MSAC review of ELT found no studies describing the prevalence of varicose veins in the general Australian population, prevalence rates for varicose veins were reported in the general community of countries with similar ethnic composition to Australia, ranging from 6.8 to 39.7 per cent in men and from 24.6 to 39.0 per cent in women. The broad range of prevalence rates was accounted for by inter-study variability of the age structure of study populations, definitions of varicose veins, and methodology used to measure venous disorders (MSAC 2003). In a 2004 health survey of the Australian population by the Australian Institute of Health and Welfare (AIHW), 2.3 per cent of all respondents reported varicose veins as a long-term condition, an estimated 440,000 people (AIHW 2004). However, as it was based on self-reports rather than physical examination and medical tests, the survey may not provide a true measure of prevalence. It also provided no information regarding the clinical severity of varicose veins reported.

Statistics from the AIHW National Hospital Morbidity Database report that in the year 2004-2005, there were 16,272 hospital admissions for the treatment of varicose veins in

lower extremities (ICD-10 Diseases I83.0, I83.1, I83.2, & I83.9).[1] In the same time period, 14,950 procedures were performed for the interruption of saphenofemoral and/or saphenopopliteal junction varicose veins using the current 'gold standard' of saphenous junction ligation with or without vein stripping (MBS items 32508 and 32511 as defined in Table 4).[2] These figures help to provide some indication of the level of clinical need for ELT in the Australian context. In Australia, it is predominantly women who seek treatment for varicose veins as shown by the prevalence of claims processed by Medicare Australia for the range of varicose vein treatments. The demand for treatment appears to peak between 35 and 64 years of age for both men and women. An example of the age and gender distribution of the claims processed by the MBS for items 32508 and 32511 is shown in Table 2.[3]

Table 2 Combined number of claims for MBS items 32508 and 32511 for treatment of varicose veins (July 2006 – June 2007)

Age range	Male	Female	Total number of MBS claims
0-4	2	0	2
5-14	2	6	8
15–24	54	75	129
25–34	182	478	660
35–44	557	1,356	1,913
45–54	697	1,435	2,132
55–64	793	1,368	2,161
65–74	428	588	1,016
75–84	110	186	296
>=85	5	13	18
Total	2,830	5,505	8,335

MBS: Medicare Benefits Schedule

Furthermore, CVD can recur after treatment; statistics from the MBS show that while 8,335 junction ligation and/or vein stripping procedures of the saphenous veins were performed during 2006-2007 (Table 2), a further 2,036 ligation and stripping procedures for the re-treatment of varicose veins were performed within the same period (Table 3; MBS items 32514 and 32517 as defined in Table 4).[4] This need for recurring treatment may place a considerable burden on health services.

[1] Retrieved August 29, 2007, from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/principaldiagnosis9899-0405

[2] Retrieved August 29, 2007 from http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/procedure0405

[3] Retrieved August 29, 2007 from http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

[4] Retrieved August 29, 2007 from http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Varicose veins are relatively common; however, it is their degree of severity that is likely to influence the demand for health services. Although the prevalence of milder forms of varicose veins is high, this may not necessarily translate to clinical burden. Clearer definitions of varicose veins that reflect degrees of severity are needed to determine prevalence rates and more accurately assess the clinical burden on the community.

Table 3 Combined number of claims for MBS items 32514 and 32517 for re-treatment of varicose veins (July 2006 – June 2007)

Age range	Male	Female	Total number of MBS claims
0–4	1	0	1
5–14	0	0	0
15–24	3	3	6
25–34	18	36	54
35–44	54	208	262
45–54	116	355	471
55–64	195	538	733
65–74	121	279	400
75–84	38	63	101
>=85	3	5	8
Total	549	1,487	2,036

MBS: Medicare Benefits Schedule

Existing procedures

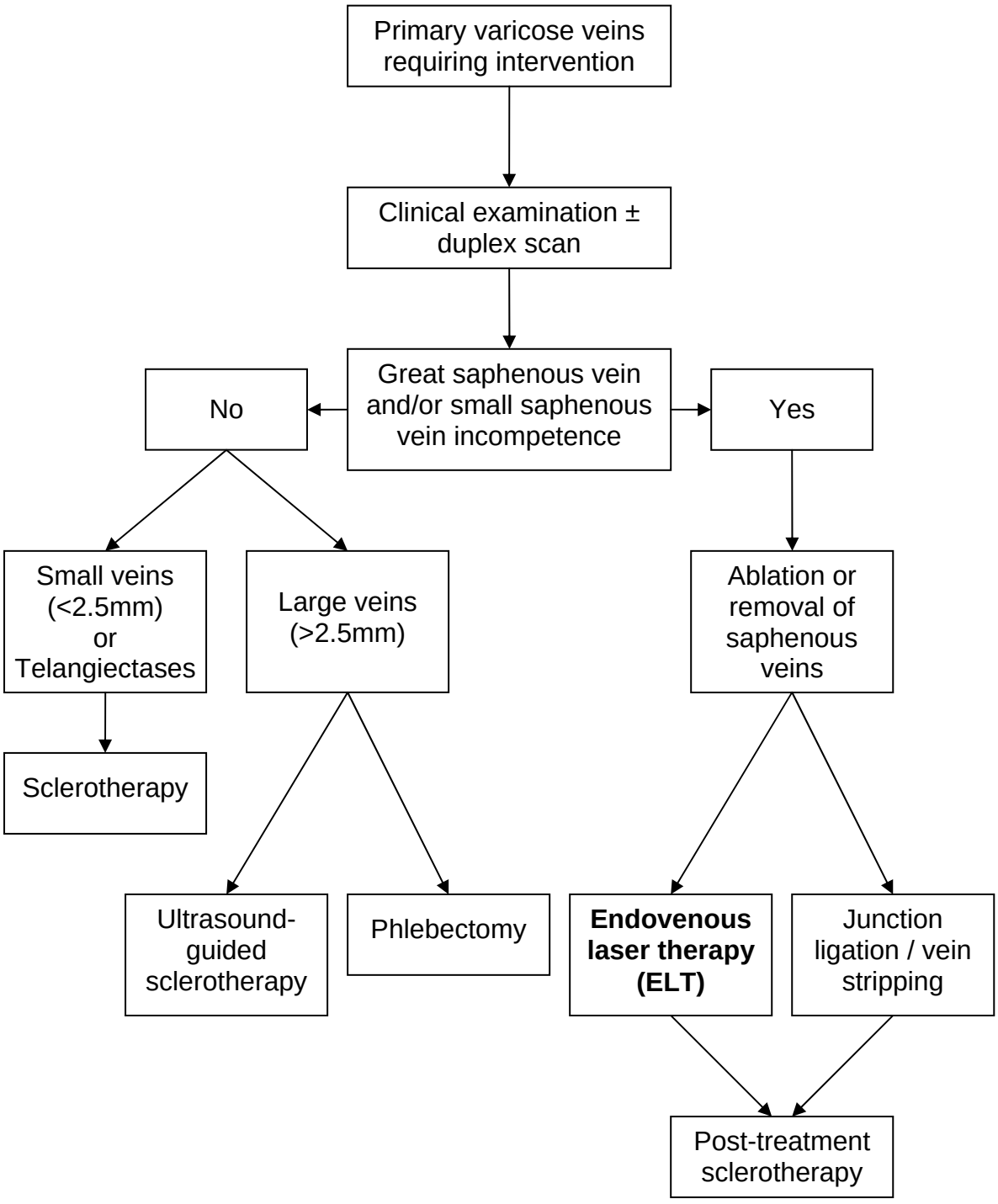
The clinical decision-making process concerned with the treatment and diagnosis of patients with varicose veins is presented in Figure 3.

A broad range of treatment options for varicose veins is available depending on the severity of symptoms and the clinical assessment of the patient. Patients require a physical examination to determine the source of venous incompetency, ideally and frequently followed by a duplex scan examination which will confirm presence of reflux (Wolf & Brittenden 2001).

Relief of symptoms may be achieved with self-help mechanisms such us exercise, weight loss, elevation of limbs, avoidance of long periods of time sitting or standing, and the use of compression stockings (Beckman 2002).

Sclerotherapy (the ablation of the vessel by the injection of a sclerosing agent) is the treatment of choice for telangiectasies or primary varicose veins where reflux has not been demonstrated. However, where reflux has been demonstrated to be the cause of vascular insufficiency, it is suggested that sclerotherapy is unlikely to give a durable result (Bergan et al 2001). Another commonly used approach to the ablation of the saphenous vein is the technique of ultrasound-guided sclerotherapy (UGS), where the sclerosing agent is injected into the refluxing vein under ultrasound guidance either as a liquid or as a foam made by forcibly mixing detergent sclerosants with air or other gases (Campbell 2002; Myers et al 2007). In addition, small non-reflux varicose veins on the surface of the leg may be treated under local anaesthetic using ambulatory phlebectomy (Bergan et al 2001; Sadick 2005).

Figure 3 Clinical decision tree for endovenous laser therapy (ELT) for varicose veins



A similar technique to ELT is the VNUS Closure system (Medical Technologies, Inc.), which utilises radio-frequency wavelengths for ablation. A heat-generating catheter is inserted into the vein and positioned below the saphenofemoral or saphenopopliteal junction. The catheter is heated to 85°C and slowly withdrawn down the length of the vein, causing contraction of the vein wall and, ultimately, destruction of the vessel (Manfrini et al 2000; Sybrandy & Wittens 2002). The VNUS technique is not currently listed on the MBS.

The mechanisms of occlusion differ between the procedures. The ELT and VNUS systems occlude the vein by generating heat, causing the vein to shrink and collapse. In sclerotherapy, a sclerosing agent (saline, aethoxysclerol or sodium tetradecyl sulphate) irritates the endothelium of the treated vein, causing it to thrombose. External compression assists in collapsing and sealing the vessel, which is eventually absorbed by the surrounding tissue.

Comparator

Endovenous laser therapy is suggested after self-help mechanisms and primary interventions have been exhausted and have failed to ease pain and prevent further damage. Therefore, the most appropriate comparator is the standard intervention currently used to treat these types of patients, specifically saphenous junction ligation with or without vein stripping.

Ligation involves tying off the vessel at either the saphenopopliteal or the saphenofemoral junction (Ruckley 1983; Wolf & Brittenden 2001). Ligation alone usually results in a high recurrence rate of the varicose vein, which may then require sclerotherapy treatment (Bergan et al 2001). In most cases, ligation is performed in conjunction with stripping for the great saphenous vein but stripping is not regularly performed for the small saphenous vein. A survey of 379 consultant members of the Vascular Society of Great Britain and Ireland found that only 14.5 per cent routinely stripped the small saphenous vein; the majority avoided this due to fear of nerve damage (Winterborn et al 2004).

Surgical ligation and stripping of the great saphenous vein for varicose veins is seen by many to be the treatment of choice (Wolf & Brittenden 2001). Stripping of the great saphenous vein involves making one or two incisions under general anaesthetic, one in the patient's groin and one at the knee or ankle. The uppermost section of the saphenous vein is ligated flush with the femoral vein and the tributary veins are ligated and avulsed, reducing the need for secondary follow-up treatment such as sclerotherapy. The stripper is inserted into the lumen of the vein and passed either down from the incision in the groin to the knee or up from an incision at the ankle to the groin. The divided end of the great saphenous vein is tied onto the head of the stripper and gentle withdrawal of the stripper pulls the saphenous vein towards the point of exit from where it can be removed (Bergan et al 2002; Lofgren 1985). Occasionally it may be difficult to pass the stripper down to the knee due to the tortuous nature of the vein and thus only a small section of the vein can be dissected at its origin (Lofgren 1985). Stripping below the knee is now generally discouraged due to an increased risk of damage to the saphenous nerve.

Perforate invagination (PIN) is a modification of conventional stripping which reduces the tissue trauma associated with pulling the conventional stripper down the vein. Rates of neuralgia, paraesthesia and haematoma appear to be reduced using the PIN method

(Durkin et al 1999; Scheltinga et al 2007). It should be noted that at present PIN stripping is not differentiated from conventional stripping on the MBS.

The technique most commonly used to treat small saphenous vein reflux is to approach the saphenopopliteal junction through a transverse incision at a level for the junction previously defined by ultrasound, ligate the vein flush with the popliteal vein and excise as much length as possible within the operative field. Only a minority of surgeons then strip the vein, either antegrade from ankle to knee or retrograde from knee to mid-calf or ankle.

Marketing status of the technology

At present, three laser systems used for ELT are registered on the Australian Register of Therapeutic Goods:

- Diomed endovenous laser treatment (EVLT; Sole Health Care Products Pty Ltd): ARTG 80883
- Biolitec endolaser vein system (ELVeS; Biolab Australia Pty Ltd): ARTG 128819
- Cooltouch endovenous (CTEV; Scanmedics Pty Ltd): ARTG 121895.

Current reimbursement arrangement

Currently there is no listing on the MBS for ELT. Sclerotherapy, phlebectomy, stripping and junction ligation of the great and/or small saphenous vein are listed on the MBS (November 1, 2007) as shown in Table 4:

Table 4 Current MBS-listed treatments for varicose veins

Procedure	MBS Item Number	MBS Listing	MBS claims (Jul 2006–Jun 2007)[a]
Sclerotherapy	32500	VARICOSE VEINS where varicosity measures 2.5mm or greater in diameter, multiple injections of sclerosant using continuous compression techniques, including associated consultation - 1 or both legs - not being a service associated with any other varicose vein operation on the same leg (excluding after-care) - to a maximum of 6 treatments in a 12-month period Fee: $99.15	55,088
	32501	VARICOSE VEINS where varicosity measures 2.5mm or greater in diameter, multiple injections of sclerosant using continuous compression techniques, including associated consultation - 1 or both legs - not being a service associated with any other varicose vein operation on the same leg (excluding after-care) where it can be demonstrated that truncal reflux in the long or short saphenous veins has been excluded by duplex examination - and that a 7th or subsequent treatment (including any treatments to which item 32500 applies) is indicated in a 12-month period Fee: $99.15	3
Phlebectomy	32504	VARICOSE VEINS, multiple excision of tributaries, with or without division of 1 or more perforating veins - 1 leg - not being a service associated with a service to which item 32507, 32508, 32511, 32514 or 32517 applies on the same leg Fee: $241.70	2,528
Stripping and/or junction ligation	32508	VARICOSE VEINS, complete dissection at the saphenofemoral OR saphenopopliteal junction - 1 leg - with or without either ligation or stripping, or both, of the long or short saphenous veins, for the first time on the same leg, including excision or injection of either tributaries or incompetent perforating veins, or both Fee: $481.85	7,425
	32511	VARICOSE VEINS, complete dissection at the saphenofemoral AND saphenopopliteal junction - 1 leg - with or without either ligation or stripping, or both, of the long or short saphenous veins, for the first time on the same leg, including excision or injection of either tributaries or incompetent perforating veins, or both Fee: $716.40	910
	32514	VARICOSE VEINS, ligation of the long or short saphenous vein on the same leg, with or without stripping, by re-operation for recurrent veins in the same territory - 1 leg - including excision or injection of either tributaries or incompetent perforating veins, or both Fee: $836.95	1,566
	32517	VARICOSE VEINS, ligation of the long and short saphenous vein on the same leg, with or without stripping, by re-operation for recurrent veins in either territory - 1 leg - including excision or injection of either tributaries or incompetent perforating veins, or both Fee: $1077.75	470
Imaging	55296	DUPLEX SCANNING, unilateral, involving B mode ultrasound imaging and integrated Doppler flow spectral analysis and marking of veins in the lower limb below the inguinal ligament prior to varicose vein surgery, not being a service associated with a service to which an item in Subgroups 1 (with the exception of item 55054), 3 or 4 of this Group applies - including any associated skin marking (R) Fee: $111.05	3,931

MBS: Medicare Benefits Schedule

[a] Claims data retrieved August 29, 2007 from http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Approach to assessment

Search strategy

The search strategy for this assessment was based on the strategy used in the previous MSAC review comparing the ELT procedure to conventional surgical junction ligation and vein stripping (MSAC 2003). However, in light of changes to the available body of literature, two separate search strategies were employed to systematically identify studies for the present review in which ELT or surgical junction ligation and vein stripping were used in the treatment of varicose veins.

PICO (population, intervention, comparator, outcome) criteria were developed with the assistance of the advisory panel to assist in specifying the search strategy (Table 5).

Table 5 PICO (population, intervention, comparator, outcome) criteria

Population	Patients with documented primary venous reflux of the great or small saphenous veins, in whom sclerotherapy is unlikely to be successful
Intervention	ELT for the treatment of saphenous reflux, incorporating lasers of all appropriate wavelengths (ie 810, 940, 980, 1064, and 1320 nm)
Comparator	Surgical saphenous stripping and/or junction ligation of varicose veins
Outcome	*Safety:* ▪ Mortality rate ▪ Post-operative infection ▪ Laser-related adverse effects ▪ Thrombotic events ▪ Pain ▪ Bleeding complications ▪ Ecchymosis ▪ Paraesthesia and nerve damage ▪ Induration ▪ Phlebitis ▪ Lymphoedema *Effectiveness:* ▪ Abolition of reflux ▪ Recurrence of varicose veins ▪ Recanalisation ▪ Symptom reduction ▪ Quality of life ▪ Time taken to resume normal activities ▪ Procedure operating time

ELT: Endovenous laser therapy

From expert clinical opinion provided by the advisory panel regarding the quantity of literature available it was decided to date limit the literature search for surgical ligation and vein stripping to relevant studies published within the past 10 years and, for case series studies only, a patient population greater than 100. As this report is an update of a previous review of ELT (MSAC 2003), it was also decided to limit the literature search for ELT to locate studies published after the literature search of the previous review was conducted. Thus the medical literature was searched to identify relevant studies and reviews for the period between January 1997 and August 2007 for surgical ligation and vein stripping, and between September 2003 and August 2007 for ELT.

Relevant electronic internet databases were searched for relevant literature up until August 2007, while updated listings of reports were located and searched at the websites of health technology assessment agencies and specialist vascular websites up until August 2007. Appendix C details the complete list of bibliographic databases, electronic internet databases and health technology assessment agency websites that were used for the search.

The search terms from the previous review were mostly retained, with those used in the systematic search listed in Table 6. It was decided to remove the 'ultrasonography, Doppler' medical subject heading (MeSH) search term from the ELT search strategy used in the previous review as ultrasound imaging is only an adjunct to the ELT procedure, albeit an important one. It was also decided to add the 'ligation' MeSH search term to the ligation and stripping search strategy to ensure studies that used ligation alone as a treatment modality would not be overlooked. The full search strategies (based on a PubMed platform) are provided in Appendix D.

Table 6 Search terms utilised

Area of inquiry	Search terms
ELT search	MeSH Venous insufficiency, Saphenous vein, Varicose veins, Laser surgery, Vascular surgical procedures Text words saphenous near vein*, varicose near vein*, venous near (reflux or incomp* or insuff*), endovenous*, laser*, EVLT, endovasc*
Ligation/stripping search	MeSH Venous insufficiency, Saphenous vein, Varicose veins, Surgical procedures (operative), Vascular surgical procedures, Ligation Text words saphenous near vein*, varicose near vein*, venous near (reflux or incomp* or insuff*), strip*, junction lig*, junction near ligation

ELT: Endovenous laser therapy; MeSH: Medical subject headings

Inclusion criteria

Since the previous review of ELT and junction ligation and vein stripping was conducted, a number of studies providing comparative data between the two procedures have been published, allowing direct comparison. Separate searches were conducted for ELT and junction ligation and vein stripping. Due to the wealth of literature, only data from studies with 100 or more patients were assessed for the safety outcomes of junction ligation and vein stripping. Case series were used for the assessment of safety outcomes only. Advisory panel opinion was that in the presence of high level evidence, lower level evidence (case reports) would not be included. Inclusion and exclusion criteria applied to the identified citations for assessing the safety and effectiveness of ELT are shown in Appendix C.

Review of literature

Literature databases

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Excluded studies are listed in Appendix E with reasons for exclusion. The bibliographies of all retrieved publications were hand-searched for any relevant references missed in the database search (pearling).

Data extraction

Data were extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information.

Description and methodological quality of included studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 7) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 7 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 8

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 8.

Table 8 Designations of levels of evidence

Level of evidence*	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Included studies were critically appraised for study quality according to the guidelines in Chapter 6 - Cochrane Reviewers' Handbook (Higgins & Green 2005). Included randomised controlled trials (RCTs) were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias, with reference to the CONSORT Statement (Altman et al 2001). Two reviewers critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. A quality score was not assigned, instead the quality of the included studies was described in a narrative fashion, and any important quality issues were highlighted in the discussion of outcomes.

Data analysis

Meta-analysis

Where outcomes of RCTs could be sensibly combined (outcomes measured in comparable ways and no apparent heterogeneity), relative risks or weighted mean differences with 95 per cent confidence intervals (CI) were calculated using RevMan 4.2 (Update Software). Relative risks or weighted mean differences were also calculated for some outcomes of individual RCTs as an aid in the interpretation of results. The confidence intervals represent a range within which the 'true' value of an effect size is expected to lie, with a given degree of certainty eg 95 per cent CI.

Subgroup analyses were carried out for certain variables where possible. Differences in the frequency of pre- and post-treatment outcomes were calculated using a chi square test, where applicable, at $P<0.05$.

Handling of non-randomised data

Where statistical pooling was not possible, medians of rates (for dichotomous outcomes) or medians of means (for continuous outcomes) were calculatred for all studies reporting the outcome.

Included studies

The studies identified as fulfilling the review inclusion criteria, stratified by level of evidence, are listed in Appendix F. Those studies which did not meet the inclusion criteria are outlined in Appendix E, along with reasons for their exclusion.

Current and recent clinical trials and health technology assessments of the use of ELT for varicose veins

Websites of clinical trials agencies were searched to identify all relevant ongoing or unpublished clinical trials related to the topics of this review. These included the Australian Clinical Trials Registry, ClinicalTrials.gov, the National Research Register (UK) and Controlled-Trials.com. As of 27 August 2007, a total of ten trials investigating the use of ELT in the treatment of varicose veins were identified; these can be found in Appendix G.

A list of electronic databases and websites of international HTA agencies can be found in Appendix C. As of 27 August 2007, a total of five health technology assessments and reviews were identified through searches of these databases and through the main search strategy of this review; these are presented in Appendix G.

Expert advice

An advisory panel with expertise in vascular surgery, ELT, radiology, general practice and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical and patient perspective (Appendix B). In selecting members for advisory panels, the practice of MSAC is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees.

Results of assessment

Descriptive characteristics of included studies

Studies for assessment of safety

ELT studies

Forty studies were identified for inclusion in the assessment of the safety of ELT. This includes five studies comparing ELT to surgical vein stripping, two studies comparing ELT to the non-MBS listed procedure of radiofrequency ablation (Marston et al 2006; Puggioni et al 2005) and three internal randomised comparative studies that compared variations within the ELT procedure such as patient position or laser wavelength (Desmyttere et al 2005; Kabnick et al 2006; Proebstle et al 2005). The analysis of internal comparative studies or the ELT arm of randomised comparative studies, in isolation, results in these studies being considered as case series and as such, any data extracted from them is considered to be Level IV evidence. The remaining 30 studies were descriptive case series and of relatively low methodological quality (Level IV evidence; see Appendix F). Sample sizes in the ELT studies ranged from 11 to 1050 patients, with 17 to 1076 saphenous veins treated respectively.

Ligation and stripping studies

Twenty-two studies were identified for inclusion in the assessment of the safety of surgical junction ligation and vein stripping. This number includes five studies comparing ELT to surgery, two randomised comparative studies that compared conventional surgery to bipolar coagulating electrical vein stripping (Lorenz et al 2007) and sclerotherapy and conservative therapy (Michaels et al 2006), as well as seven internal comparative studies comparing specific points of surgery such as conventional versus inversion stripping, partial versus full stripping, ligation technique and post-operative therapies (Biswas et al 2007; Butler et al 2007; Canonico et al 2000; Frings et al 2004; Herman et al 2002; Hulusi et al 2006; Nisar et al 2006). As with ELT, the analysis of internal comparative studies and the surgical arm of randomised controlled trials, in isolation, results in these studies being considered as case series and as such, any data extracted from them is considered to be Level IV evidence. The remaining eight studies were descriptive case series of relatively low methodological quality (Level IV evidence; see Appendix F). Sample sizes in the surgical studies ranged from 100 to 1261 patients, with 100 to 1638 saphenous veins treated respectively.

Studies for assessment of effectiveness

The systematic literature search revealed a total of five studies that directly compared the use of ELT to conventional junction ligation and stripping for the treatment of varicose veins (de Medeiros 2006; Mekako et al 2006b; Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005). These studies allowed the assessment of the comparative effectiveness of the procedures within this review. Two of these studies were randomised controlled trials (de Medeiros 2006; Rasmussen et al 2007) (Level II evidence) while the remaining three were non-randomised experimental trials (Level III evidence) that either treated patients with ELT and surgery across different time points within the study period (Mekako et al 2006b; Wu et al 2005) or did not report the method of patient allocation (Vuylsteke et al 2006). Sample sizes in the five comparative studies ranged from 20 to 164, with 40 to 246 saphenous veins treated respectively. The study by Wu et

al (2005) required translation into English from Chinese. A subsequent section will examine these studies in greater detail and appraise their methodological quality.

Duplication of results

Possible duplication of results may have occurred in the ELT studies of Kim and colleagues (Kim et al 2006; Kim & Paxton 2006), Proebstle et al (2003, 2005, 2006) and Timperman et al (2004, 2005), and the ligation studies by Chang et al (2002, 2006). However, this was not clearly stated and could not be determined as only one study (Timperman et al 2004) explicitly reported the time period of the study. The ELT study by Ravi et al (2006) was a longer-term follow-up study to that of Perkowski et al (2004).

Systematic reviews

One systematic review of ELT as a treatment for varicose veins was published in 2005 (Mundy et al 2005); this review was based on the findings of the previous MSAC report that this review updates (MSAC 2003). The authors reported there were no controlled studies available that assessed the effectiveness of ELT in comparison to saphenofemoral ligation with saphenous vein stripping. Thus, this systematic review cannot be regarded as level I evidence. The authors concluded that although ELT appeared beneficial, until the results of a comparative trial of ELT and surgical ligation and vein stripping become available it should be considered as an experimental treatment.

Descriptive characteristics of comparative studies

Of the five comparative studies that compare the use of ELT to surgery (de Medeiros 2006; Mekako et al 2006b; Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005), one was conducted in each of Brazil, the United Kingdom, Denmark, Belgium and China (Table 9). The study by Wu et al (2005) was published in Chinese and required translation to English; this made it difficult to fully ascertain all relevant study information and it is possible that some amount of information regarding the study and procedural methodology was lost in this translation.

The study of de Medeiros (2006) presented mid-term results of a randomised controlled trial originally published the previous year (de Medeiros & Luccas, 2005). While the updated study had a mean follow-up period of 26 months compared to 9 months in the initial study, it reported very little new data. A total of 40 limbs were treated, 20 receiving ELT and 20 receiving ligation and stripping. Mekako et al (2006b) presented the results of a non-randomised comparative pilot study (12-week follow-up) of 132 patients treated with ELT (70 patients) or ligation and stripping (62 patients). Rasmussen et al (2007) presented short-term results (maximum follow-up of 6 months) of a randomised controlled trial of 121 patients treated with ELT (62 patients, 69 limbs) or ligation and stripping (59 patients, 68 limbs). The study by Vuylsteke et al (2006), with a maximum follow-up of 9 months, compared the results of 164 patients treated with ELT (80 patients, 118 limbs) or surgical ligation and vein stripping (84 patients, 128 limbs). Wu et al (2005) reported the results of a non-randomised comparative study comparing ELT (20 patients, 22 limbs) to traditional surgery for varicose veins (30 patients, 36 limbs), with a maximum follow-up of 12 months.

MSAC generally uses procedures currently listed on the MBS schedule as comparators. Studies comparing ELT to a non-MBS listed treatment, such as radiofrequency ablation, were not used to provide evidence of the relative effectiveness of ELT. These studies are retained only to provide information about safety outcomes for ELT alone, and are treated as case series for the purposes of this review. Full descriptive characteristics of the five comparative studies with the MBS-listed comparator of surgical ligation and vein stripping are listed in Table 9.

Table 9 Descriptive characteristics of comparative studies

Study	Study design (NHMRC level of evidence)	Study period	Follow-up	Inclusion criteria	Exclusion criteria
de Medeiros (2006) Campinas, BRAZIL	Randomised controlled trial (Level II)	March 2002 – February 2004	Mean: 26 months Range: 4.5-35.5 months	Symptomatic, varicose veins on both lower limbs, bilateral insufficiency of the entire GSV on duplex scanning	Congenital varicose veins, secondary varicose veins, recurrent varicose veins, history of deep venous thrombosis, deep venous system changes, anatomical malformations, peripheral obstructive arterial disease, pregnancy
Mekako et al (2006b) Hull, UNITED KINGDOM	Non-randomised experimental trial (Level III-2)	NR	12 weeks	NR	NR
Rasmussen et al (2007) Naestved, DENMARK	Randomised controlled trial (Level II)	August 2005 – July 2006	6 months	Varicose veins of CEAP class C2-C4 with etiology: primary, anatomy: superficial and pathophysiology: reflux, age 18-80 years, GSV incompetence defined by reflux time > 0.5sec by ultrasound imaging	Duplication of the saphenous trunk or an incompetent anterior accessory GSV, SSV reflux until 3 months after removal of such vein, previous deep venous thrombosis, history of arterial insufficiency or ankle-brachial index < 0.9 or both, axial deep venous insufficiency (femoral or popliteal vein or both), excessively tortuous GSV
Vuylsteke et al (2006) Tielt, BELGIUM	Non-randomised experimental trial (Level III-2)	January 2002 – December 2003	9 months	Patients with CEAP clinical class C2-C4 varicose veins caused by GSV insufficiency, working full-time	Associated peripheral occlusive or inflammatory arterial disease, known thrombotic or haemorrhagic tendency (also oral anticoagulation), history of irradiating low back pain, pregnancy or planning to become pregnant, venous diameter > 20mm, dilation from the SFJ with multiple insufficient side branches
Wu et al (2005) Guangzhou, CHINA	Non-randomised experimental trial (Level III-2)	January 2003 – April 2004	12 months	NR	NR

CEAP: Clinical, etiology, anatomy, pathophysiology; GSV: Great saphenous vein; NR: Data not reported; SFJ: Saphenofemoral junction; SSV: Small saphenous vein

Critical appraisal of comparative studies

Inclusion and exclusion criteria

Inclusion and exclusion criteria for the recruitment of patients in each of the studies are displayed in Table 9. Explicit inclusion and exclusion criteria could only be obtained from three of the five studies; inclusion or exclusion criteria could not be ascertained from the studies by Mekako et al (2006b) or Wu et al (2005). Inclusion criteria generally entailed reflux in the great saphenous vein, while exclusion criteria consisted mainly of clinical and physiological characteristics that would contraindicate the treatment of varicose veins with ELT or surgery, such as arterial disease, thrombotic or haemorrhagic history, anatomical malformations such as a tortuous saphenous vein, or pregnancy. Two studies restricted veins included in the study to CEAP classes C2 to C4 (Rasmussen et al 2007; Vuylsteke et al 2006), while Rasmussen et al (2007) was the only study to place age restrictions on patients.

Validity characteristics of comparative studies

A summary of the quality of the five studies used in this review comparing ELT to surgery for the treatment of varicose veins is provided in Appendix H. The criteria used were based on the CONSORT statement of Altman et al (2001).

Regarding study design, Rasmussen et al (2007) randomised patients to treatments using blocks of 10 sealed envelopes, while de Medeiros (2006) determined the procedure to be used on each limb by drawing lots, although no more information on this randomisation is given. Patients in the studies by Mekako et al (2006b) and Wu et al (2005) were determined historically, treated with ligation and stripping until ELT treatment was available and offered, at which point ELT became the treatment of choice. Vuylsteke et al (2006) did not report allocation details. Only two studies attempted to blind patients or examiners during the study; in the study by de Medeiros (2006), patients were blinded to the treatment used on each limb while examiners conducting clinical follow-up were blinded to the study data. Vuylsteke et al (2006) blinded patients' general practitioners to the fact that duration of sick leave was an outcome of the study.

Groups were well matched at baseline for demographic and clinical characteristics in all five studies; however Mekako et al (2006b) reported a number of significant differences in baseline scores on self-report scales of quality of life and varicose symptoms. These differences will be discussed later in more detail. While four studies adequately described interventions used, the study by Wu et al (2005) failed to report the procedure used for surgical stripping, describing the procedure simply as conventional surgery involving severing of the saphenous vein. Primary outcomes were defined in all studies, with the exception of Wu et al (2005).

In terms of reporting of results, only Rasmussen et al (2007) reported their analysis technique, choosing to compare treatment groups on an intention-to-treat basis. Four of the comparative studies detailed the statistical tests that were used, while these details were not obtained for Wu et al (2005). All five studies utilised appropriate statistical methods, tests and significance levels. There were some issues regarding reporting of outcomes and adverse events; Mekako et al (2006b) did not stratify clinical occlusion outcomes by treatment and reported adverse events in very little detail, Vuylsteke et al (2006) reported findings for unilaterally- and bilaterally-treated patients independently of

one another, and Wu et al (2005) grouped adverse events and did not provide incidence rates of individual complications.

Follow-up and losses to follow-up

Maximum follow-up amongst the five comparative studies ranged from 12 weeks in the pilot study by Mekako et al (2006b) to 26 months (de Medeiros 2006), as shown in Appendix H. Mekako et al (2006b) lost to follow-up 21 patients from the ELT group and 33 from the surgical vein stripping group, while Rasmussen et al (2007) lost to follow-up 15 ELT-treated limbs and 18 limbs treated with surgical vein stripping. Rasmussen et al (2007) did not report the actual number of patients lost to follow-up, and neither study reported causes of patient dropout. The remaining studies did not report any patients lost to follow-up.

Patient characteristics of comparative studies

Table 10 summarises the patient population characteristics across the five comparative studies. Patient group characteristics were generally well matched within each of the studies; however, Mekako et al (2006b) reported a number of significant differences between ELT and stripping treatment groups in baseline scores on the SF-36 quality of life scale, Aberdeen Varicose Veins Questionnaire (AVVQ) and Venous Clinical Severity Score (VCSS). Patients in the surgical group reported significantly poorer quality of life in the SF-36 domains of physical functioning (P=0.003), bodily pain (P=0.009) and vitality (P=0.009), and significantly worse varicose symptoms on the AVVQ (P=0.001) and VCSS (P<0.001) before treatment. While these baseline differences were appropriately adjusted for through the statistical method of analysis of covariance (ANCOVA), they should be taken into consideration when interpreting the findings as potentially distorting the results.

Patient characteristics appeared comparable across studies. Study populations were predominantly female, with mean age of participants generally similar across studies, although the mean age of patients in the study by Vuylsteke et al (2006) was slightly younger than in the other studies. Distribution of CEAP classification varied slightly between studies; however, the majority of patients treated were in classes C2-C4, with few (or in some cases, no) patients from classes C5 and C6, both of which indicate the presence of venous ulcers. Only two studies reported mean diameter of the great saphenous vein (de Medeiros 2006; Rasmussen et al 2007), with both reporting similar values. Where reported in studies, all included patients presented with primary and/or superficial reflux.

Table 10 Patient characteristics of comparative studies

Study	Intervention group	Number of patients (limbs treated)	Gender (M/F)	Mean age (range) in years	CEAP classification n (%)					Mean GSV diameter (mm) Mean ± SD (range)
					2	3	4	5	6	
de Medeiros (2006)	ELT	20 (20)[a]	1/19	46 (23-71)	9 (45)	2 (10)	3 (15)	4 (20)	2 (10)	8.23±2.16 (5.0-11.3)
	L/S	20 (20)[a]	1/19	46 (23-71)	11 (55)	5 (25)	3 (15)	1 (5)	0 (0)	8.50±2.23 (5.0-12.0)
	P value		-	-	NS					NS
Mekako et al (2006b)	ELT	70	33/37	49 (35-58)[b]	45 (64)	0 (0)	24 (34)	1 (1)	0 (0)	-
	L/S	62	19/43	49 (35-61)[b]	41 (66)	3 (5)	16 (26)	2 (3)	0 (0)	-
	P value		NS	NS	-					
Rasmussen et al (2007)	ELT	62 (69)	21/41	53 (26-79)	50 (81)	3 (5)	9 (15)			7.9±2.7 (3-16.5)
	L/S	59 (68)	16/43	54 (22-78)	51 (86)	5 (8)	3 (5)			7.6±2.1 (4-13)
	P value		-	-	-					-
Vuylsteke et al (2006)[c]	ELT	80 (118)	29/51	40	2.5					-
	L/S	84 (128)	25/59	41	2.4					-
	P value		NS[d]	NS[d]	NS[d]					
Wu et al (2005)	ELT	20 (22)	8/12	55.4 (25-79)	3 (14)	8 (36)	7 (32)	2 (9)	2 (9)	-
	L/S	30 (36)	12/18	52.2 (22-75)	6 (17)	8 (22)	12 (33)	6 (17)	4 (11)	-
	P value		NS	NS	NS					

CEAP: Clinical, etiology, anatomy, pathophysiology; ELT: Endovenous laser therapy; NS: Non-significant; L/S: ligation/stripping; -: Data not reported

Plus-minus values are mean ± standard deviation; filled areas denote CEAP classifications excluded by study criteria

[a] All 20 patients received both treatments

[b] Values are median and (inter-quartile range)

[c] Vuylsteke et al (2006) reported patient characteristics separately for unilaterally- and bilaterally-treated patients; values are approximate means from combined patient data

[d] No significant differences found between ELT and L/S within unilaterally- and bilaterally-treated patient groups

Technical details of comparative studies

Technical details of ELT procedures and surgical ligation and stripping comparators are provided in Table 11 and Table 12. De Medeiros (2006) was the only study that specifically reported ligating the great saphenous vein before ELT ablation. The study by de Medeiros (2006) was also procedurally unique in that all 20 patients received both ELT and stripping, with ELT performed on one leg and stripping on the other. There was some variety in the ELT equipment and parameters (laser wavelength, power, energy delivery mode) used across studies; three studies used an 810 nm laser wavelength (de Medeiros 2006; Mekako et al 2006b; Wu et al 2005) while two used a 980 nm wavelength (Rasmussen et al 2007; Vuylsteke et al 2006). Power generally ranged from 10 to 14 watts but de Medeiros (2006) went as low as 4 watts when decreasing power along the course of the saphenous vein. Mekako et al (2006b) was the only study that used continuous energy to occlude the vein with the remainder using bursts or pulsed energy. One study ablated the great saphenous vein from ankle to groin (de Medeiros 2006), two ablated the great saphenous vein from groin to knee (Mekako et al 2006b; Rasmussen et al 2007) and Vuylsteke et al (2006) ablated the vein to the most distal point of reflux in the vein.

All studies, with the exception of de Medeiros (2006), reported use of some form of tumescent perivenous anaesthetic before application of ELT laser energy, although Wu et al (2005) referred to what could be best translated as local anaesthesia along the course of the lower limb. In total, four studies used some form of local anaesthesia (one of which, Rasmussen et al (2007), also used light sedation) while one study performed all procedures under general anaesthesia (Vuylsteke et al 2006) and one used regional anaesthesia (de Medeiros 2006).

All five studies reported use of avulsion or phlebectomy during the ELT procedure for the treatment of varicose tributaries. Further to this, de Medeiros (2006) also ligated insufficient perforator veins. With regards to previous treatment for varicosities, Rasmussen et al (2007) reported eight ELT patients had previously undergone high ligation of the great saphenous vein. In the study by Wu et al (2005), seven patients underwent pre-ELT treatment for venous ulcers; four had received subfascial endoscopic perforator surgery (SEPS), two had received perforator ligation, and one had undergone laser treatment. One patient with high-grade reflux underwent valvuloplasty (valve reconstruction) treatment before ELT.

Examining the surgical comparators, it was not possible to determine the exact procedure used by Wu et al (2005); however, the description of the procedure as conventional surgery with cutting of the saphenous vein implies that ligation was used in conjunction with stripping of the vein. Of the four remaining comparative studies, all performed ligation of the great saphenous vein at or near the level of the saphenofemoral junction before stripping of the saphenous vein. Three used some form of inversion stripping of the vein (Mekako et al 2006b; Rasmussen et al 2007; Vuylsteke et al 2006) while de Medeiros (2006) did not specify the stripping technique used. Regarding the proportion of saphenous vein stripped, all studies stripped the same proportion of the vein as they ablated with ELT; de Medeiros (2006) stripped the vein from groin to ankle, Vuylsteke et al (2006) stripped the vein to the most distal point of reflux in the vein, and Mekako et al (2006b) and Rasmussen et al (2007) stripped only from groin to knee level.

Two studies performed ligation and stripping procedures under general anaesthesia (Mekako et al 2006b; Vuylsteke et al 2007), one used regional anaesthesia (de Medeiros 2006), and one used local anaesthetic with sedation (Rasmussen et al 2007).

Concurrent treatments were generally the same for ELT and stripping treatment groups; all studies except Wu et al (2005) reported use of avulsion or phlebectomy during the ELT procedure for the treatment of varicose tributaries, and de Medeiros (2006) also ligated insufficient perforators. Previous varicose vein treatments were also similar; eight surgery patients in the study by Rasmussen et al (2007) had previously undergone high ligation of the great saphenous vein. In the study by Wu et al (2005), nine patients underwent treatment for venous ulcers before surgical stripping; three had received SEPS and six had undergone perforator ligation. Two patients with high-grade reflux underwent valvuloplasty before stripping.

Table 11 Technical details of ELT techniques

Study	Laser wavelength (nm)	Power (W)	Laser energy delivery mode	Rate of laser fibre pullback	Energy delivered to vein (J/cm)	Anaesthetic	Concurrent treatments
de Medeiros (2006)	810 600µm laser fibre	Range: 4 – 12; decreasing along length of GSV	1 second pulses at 1 second intervals	5 mm increments per retraction	NR	Subarachnoid block anaesthesia (n=13, 65%) Epidural block anaesthesia (n=7, 35%)	Pre-procedure: High ligation of GSV and tributaries Post-procedure: Miniphlebectomy of varicose veins Ligation of all insufficient perforating veins
Mekako et al (2006b)	810 600µm laser fibre	14	Continuous	NR	NR	Perivenous local anaesthetic (0.2% lidocaine with 1:200,000 adrenaline) infiltrated along GSV before ablation	Post-procedure: Avulsion of varicose tributaries Diclofenac (50 mg, 3 times daily)
Rasmussen et al (2007)	980	12	1.5 second pulses at 1.5 second intervals	NR	Mean: 73.5±7.9 Range: 57-95.4	Light sedative (midazolam and alfentanil or diazepam) given pre-procedure Tumescent local anaesthetic (lidocaine 4 mg, adrenaline 4 µg, disodium-EDTA 0.5 mg, saline 8.2 mg in 1 mL sterile water with 1 ml sodium bicarbonate 84 g/L per 10 ml solution) infiltrated along GSV before ablation	Post-procedure: Varicosities removed with miniphlebectomies Diclofenac (50 mg) to be used as necessary
Vuylsteke et al (2006)	980	Maximum: 10; decreasing according to GSV diameter and distance to skin	3 second pulse at groin; pulse duration decreasing according to GSV diameter and distance to skin	2-3 mm increments per retraction	NR	All procedures performed under general anaesthetic Perivenous local anaesthetic (1/25 diluted 2% xylocaine) infiltrated along GSV before ablation	Post-procedure: Phlebectomy if required Patients given prescription for non-steroidal analgesic
Wu et al (2005)	810	12	1 second pulses at 1 second intervals	3-5 mm per second	NR	Local along lower limb	Pre-treatment: Patients with venous ulcers (n=7) underwent either SEPS (n=4), perforator ligation (n=2) or laser treatment in (n=1) Patients with high-level reflux (n=1) underwent valvuloplasty Post-treatment: Tributaries treated in same procedure as ELT

ELT: Endovenous laser therapy; GSV: Great saphenous vein; NR: Data not reported; SEPS: Subfascial endoscopic perforator vein surgery
Plus-minus values are mean ± standard deviation

Table 12 Description of surgical vein ligation and stripping techniques

Study	Comparator details	Anaesthetic	Concurrent treatments
de Medeiros (2006)	Ligation: High ligation of GSV and tributaries Stripping: Stripping of GSV from groin to ankle	Subarachnoid block anaesthesia (n=13, 65%) Epidural block anaesthesia (n=7, 35%)	Post-treatment: Miniphlebectomy of varicose veins Ligation of all insufficient perforating veins
Mekako et al (2006b)	Ligation: Ligation of SFJ Stripping: Inversion stripping of GSV from groin to knee	General anaesthetic Local anaesthetic (10 ml 1% lidocaine) injected into groin wound	Post-treatment: Multiple stab phlebectomies Diclofenac (50 mg, 3 times daily)
Rasmussen et al (2007)	Ligation: Flush ligation of SFJ; division of tributaries behind second level of the division Stripping: Perforate invagination (inversion) stripping of GSV from just below knee or most distal point of GSV reflux in the thigh to SFJ; if vein broke, attempts made to remove it through separate access below knee	Light sedative (midazolam and alfentanil or diazepam) given pre-procedure Tumescent local anaesthetic (lidocaine 4 mg, adrenaline 4 µg, dinatriumedta 0.5 mg, saline 8.2 mg in 1 mL sterile water with 1 ml natrium bicarbonate 84 g/L per 10 ml solution) infiltrated along GSV before ablation	Post-treatment: Varicosities removed with miniphlebectomies Diclofenac (50 mg) to be used as necessary
Vuylsteke et al (2006)	Ligation: Ligation of SFJ (pre-procedure) and insufficient calf perforators (post-procedure) Stripping: Inversion stripping of GSV from groin to most distal point of GSV insufficiency	All procedures performed under general anaesthetic	Post-treatment: Insufficient calf perforators ligated Phlebectomy if required Patients given prescription for non-steroidal analgesic
Wu et al (2005)	Little detail provided for technique given, described as conventional surgery for varicose veins with 'cutting' of vein. This is most likely ligation and stripping of GSV.	NR	Pre-treatment: Patients with venous ulcers (n=9) underwent either SEPS (n=3) or perforator ligation (n=6) Patients with high-level reflux (n=2) underwent valvuloplasty

GSV: Great saphenous vein; NR: Data not reported; SEPS: Subfascial endoscopic perforator vein surgery; SFJ: Saphenofemoral junction

Is it safe?

Patient and procedural characteristics of included studies

Forty studies in total were identified in which patients with varicose veins were treated with ELT (Appendix F). The allocation methods of the five studies that directly compared ELT to surgical vein stripping are reported previously. Safety outcomes and morbidities were reported clearly and stratified by treatment in three of the five comparative studies (de Medeiros 2006; Rasmussen et al 2007; Vuylsteke et al 2006), and are shown in Appendix H. Mekako et al (2006b) did not report adverse events in detail, while Wu et al (2005) reported adverse events cumulatively without presenting separate occurrence rates for each type of adverse event.

Of the 35 case series, the studies by Beale, Mavor and Gough (2006), Gibson et al (2007), Huang et al (2005), Kabnick et al (2006), Kavuturu et al (2006), Kim et al (2006), Kim and Paxton (2006), Myers et al (2006), Puggioni et al (2005) and Timperman et al (2005) used consecutive patients. Twenty-two studies were identified in which patients were treated with surgical ligation and/or vein stripping for varicose veins, including the five comparative studies examined previously; of the 17 case series, the studies by Frings et al (2004) and Mofidi et al (2000) both used consecutive patients.

A summary of patient population characteristics and procedural details of ELT and surgical ligation and stripping for all included studies is provided in Table 13. Sex and age characteristics, as well as average great saphenous vein diameter, were comparable across ELT and stripping studies. Average length of the great saphenous vein treated with ELT varied somewhat, with study means ranging from 17 to 41cm. Length of vein treated was not reported in any of the studies that used junction ligation and stripping. There was some notable disparity in CEAP classification characteristics between ELT and ligation and stripping; ELT was performed on more patients of CEAP grade C2 (simple varicose veins only) and the more severe grade C6 (presence of open venous ulcer).

In the majority of studies, ELT was performed on the great saphenous vein alone. However, there were a number of exceptions; three studies performed ELT on the great, small, and accessory saphenous veins (Agus et al 2006; Perkowski et al 2004; Timperman et al 2004), two on the great and accessory saphenous veins (Corcos et al 2005; Timperman et al 2005), six on the great and small saphenous veins (Gibson et al 2007; Myers et al 2006; Puggioni et al 2005; Ravi et al 2006; Sadick et al 2004; Viarengo et al 2006), and one on the small saphenous vein alone (Theivacumar et al 2007). Of those studies that performed ELT on the great saphenous vein, 23 performed ELT from groin to knee level, three from groin to ankle, and one performed ELT of the great saphenous vein from both groin to knee and groin to ankle. The studies by Agus et al (2006), Gibson et al (2007), Leelaudomlipi et al (2005), Myers et al (2006), Perkowski et al (2004), Petronelli et al (2006), Proebstle et al (2003, 2005, 2006), Ravi et al (2006), Vuylsteke et al (2006) and Wu et al (2005) did not explicitly report the portion of leg treated with ELT. The comparative study by de Medeiros (2006) and the studies by Corcos et al (2005) and Huang et al (2005) used ligation at the saphenofemoral junction in conjunction with ELT in at least some members of their patient population.

Table 13 Summary of patient characteristics and procedural details of all ELT and surgical ligation and stripping studies included for review

	ELT				Ligation/stripping			
	Total	Mean	Median	Range	Total	Mean	Median	Range
Number of studies	40				22			
Study follow-up (months)[a]		10.1	7.4	0.25-36		19.6	9.0	0.25-80.4
Number of patients	4525				6317			
Number of limbs treated	6575				7645			
Sex								
Male	1238				882			
Female	3115				2497			
Age (years)[a]		51.4	52.4	40.0-59.1		49.8	49.6	39.0-58.4
GSV diameter (mm)[a]		9.0	8.3	6.2-13.0		8.0	8.0	7.6-8.5
GSV treated length (cm)[a]		31.4	31.5	17.0-41.0		-	-	-
CEAP classification								
C0	0				10			
C1	0				13			
C2	2239				578			
C3	679				549			
C4	791				592			
C5	175				115			
C6	154				4			
Veins treated								
Great saphenous vein	6187				7645			
Small saphenous vein	585				-			
Accessory saphenous vein	50				-			
Section of GSV treated								
Groin – knee	1644				3456			
Groin – ankle	994				1306			
Ligation alone	-				2004			
Anaesthetic used (number of studies)								
General	4				10			
Regional	7				4			
Tumescent / Local	38				5			

CEAP: Clinical, etiology, anatomy, pathophysiology; ELT: Endovenous laser therapy; GSV: Great saphenous vein; –: Data not reported

[a] Values based on study measures of central tendency (ie means, medians)

Three studies used ligation of the great saphenous vein alone, without subsequent stripping of the vein (Chang et al 2002, 2006; Frings et al 2004). Ten of the studies involving stripping of the great saphenous vein were performed from groin to knee, two studies stripped the great saphenous vein from groin to ankle, and four studies performed stripping of the great saphenous vein from both groin to knee or groin to ankle. The studies by Ahmad et al (2006), Vuylsteke et al (2006) and Wu et al (2005) did not report numbers of patients who experienced groin to knee or groin to ankle surgery. Junction ligation and vein stripping was performed on the great saphenous vein alone in the majority of studies; however, one study also performed stripping on the small saphenous vein, but did not report the number of patients or veins receiving this treatment (Michaels et al 2006).

Summary of adverse events across included studies

For convenience, the total adverse events reported across all studies were summarised into 19 categories and grouped by type (Table 14). The list of studies that reported on each category of adverse event is provided in Appendix I.

Table 14 Summary of adverse events reported by all ELT and surgical ligation and vein stripping studies included for review

	ELT			Ligation / Stripping		
Adverse event	Studies n	Limbs (patients) n	Affected limbs n (%)	Studies n	Limbs (patients) n	Affected limbs n (%)
Total	40	6575 (4525)		22	7645 (6317)	
Thromboembolic events						
Pulmonary embolism	12	1859 (1403)	1 (0.1)	3	979 (822)	0 (0.0)
Deep venous thrombosis	24	5021 (3222)	20 (0.4)	8	1965 (1769)	30 (1.5)
Superficial thrombophlebitis[a]	11	1982 (1709)	32 (1.6)	1	100 (100)	7 (7.0)
Nerve events						
Nerve injuries[b]	13	2057 (1492)	17 (0.8)	3	946 (924)	23 (2.4)
Paraesthesia	19	3405 (2943)	129 (3.8)	8	1362 (1251)	117 (8.6)
Infection events						
Infection/Cellulitis	7	1046 (731)	3 (0.3)	10	2672 (2418)	63 (2.4)
Stitch sinus	0	-	-	1	156 (124)	8 (5.1)
Bleeding events						
Bleeding complications	0	-	-	2	892 (892)	5 (0.6)
Haematoma	10	1926 (1638)	44 (2.3)	10	3411 (2955)	240 (7.0)
Ecchymosis/Bruising	16	2820 (2419)	1437 (51.0)	5	719 (608)	152 (21.1)
Laser events						
Skin burns	21	3964 (3140)	19 (0.5)	0	-	-
Pain events						
Post-procedural pain[c]	13	2284 (2078)	533 (25.6)	5	1043 (991)	70 (7.1)
Other events						
Phlebitis	7	1285 (932)	95 (7.4)	4	2103 (1520)	94 (4.5)
Induration	6	880 (688)	411 (46.7)	0	-	-
Sensation of tightness	4	218 (189)	54 (24.8)	0	-	-
Hyperaemia	1	150 (150)	39 (26.0)	0	-	-
Oedema	2	97 (73)	5 (5.2)	1	20 (20)	8 (40.0)
Hyperpigmentation/dyschromia	7	2439 (1979)	65 (2.7)	2	631 (631)	9 (1.4)
Lymphorrhea/seroma	0	-	-	3	972 (920)	5 (0.5)

ELT: Endovenous laser therapy; –: Data not reported

[a] Superficial thrombophlebitis also includes superficial venous thrombosis

[b] Nerve injuries contain foot drop, neuritis, neuralgia, sural nerve palsy

[c] Occurrence rate calculations based on number of patients

The majority of adverse events related to treatment of varicose veins were relatively minor, making it difficult to report events in a distinct order of severity. For example, some of the most commonly reported adverse events for ELT included bruising and ecchymosis (51.0 per cent across 16 studies), induration along the course of the great saphenous vein (46.7 per cent across six studies) and a sensation of tightness in the treated limb (24.8 per cent across four studies). The most common for ligation and stripping included bruising and ecchymosis (21.1 per cent across five studies). However, it must be noted that some adverse events reported have the potential for very serious consequences or require hospital admission for treatment. For the purposes of this review, thromboembolic events in the deep venous system, nerve injury or damage, bleeding complications and infections were considered to be serious post-procedural morbidities as they are generally require specific post-operative treatment for resolution. Reported adverse events are examined in greater detail below.

Thromboembolic events

Generally speaking, the most potentially severe adverse events reported related to post-treatment formation of emboli, or thrombosis in the deep venous system.

Comparative studies

One of the five comparative studies reported a thromboembolic complication (Appendix H); Rasmussen et al (2007) reported one case (5.0 per cent) of an ELT patient presenting with extension of the saphenous thrombosis into the femoral vein, which dissolved spontaneously without anticoagulants. No statistical comparison was made between ELT and surgery regarding this complication.

All studies

One case of pulmonary embolism was reported after treatment with ELT (0.1 per cent across 12 studies); Myers et al (2006) reported no deep venous thrombosis was identified in this patient and no long-term consequences occurred. No cases of pulmonary embolism were reported after surgical ligation and stripping across the three studies that reported on this outcome.

Twenty cases of deep venous thrombosis after ELT were reported (0.4 per cent across 24 studies). Thirteen cases involved the small saphenous vein, with non-occlusive thromboses extending into the popliteal vein from the saphenopopliteal junction; twelve of these were reported in the study by Gibson et al (2007). The remaining seven cases primarily involved a non-occlusive extension of the great saphenous vein thrombus into the common femoral vein. The majority of thromboses resolved spontaneously without further treatment, while Marston et al (2006), Puggioni et al (2005) and Timperman et al (2004) administered heparin and anticoagulants for their treatment. While not reported in the table above, Viarengo et al (2006) reported that five patients experienced extension of thromboses from the great saphenous vein to the common femoral vein, which the researchers classified separately from deep venous thrombosis.

Thirty cases of deep venous thrombosis were reported after ligation and stripping (1.5 per cent across eight studies). Twenty of these cases were reported in the study by van Rij et al (2004), four of which had a previous history of deep venous thrombosis; eighteen thromboses were located in calf veins and two in the popliteal vein. Rates of resolution were generally not reported, and Hulusi et al (2006) was the only study to report using anticoagulants as treatment.

ELT studies reported a total of 32 cases of superficial thrombophlebitis (including superficial venous thrombosis) after ELT (1.6 per cent across 11 studies). Cases generally resolved quickly and spontaneously, with two studies reporting use of non-steroidal anti-inflammatories to assist resolution (Mekako et al 2006a; Oh et al 2003). One ligation and stripping study reported on superficial thrombophlebitis, finding seven cases (7.0 per cent in one study).

Nerve injury and paraesthesia

It should be noted here that some studies did not explicitly define paraesthesia as an outcome, instead reporting events as 'numbness' or 'sensory deficit' in the limb; it was decided that provided their description was appropriate, these cases were best grouped under the general complication of paraesthesia.

Comparative studies

Three comparative studies reported paraesthesia as a post-procedural complication (Appendix H). The study from de Medeiros (2006) reported one case (5.0 per cent) in a patient treated with surgery, which completely resolved in one month. Vuylsteke et al (2006) found 28 cases (22.6 per cent) of paraesthesia amongst the stripping group compared to 14 (11.9 per cent) in the ELT group. Neither of these studies performed statistical comparison between ELT and ligation and stripping. Rasmussen et al (2007) reported one self-limiting case of paraesthesia in both the ELT (1.6 per cent) and ligation and stripping (1.7 per cent) groups; no significant difference between the treatment groups was found.

All studies

A total of 17 cases of nerve injury were reported after ELT (0.8 per cent across 13 studies). These included one case each of neuralgia, sural nerve palsy and saphenous nerve damage. The remaining 14 were cases of neuritis, 12 of which were reported by Soracco et al (2005). Viarengo et al (2006) reported severe neuritis was treated with tricyclic antidepressants and after-effects persisted from 4 to 8 months. Myers et al (2006) reported resolution after 6 months, while Sharif et al (2006) reported saphenous nerve damage had not resolved after 12 months.

In contrast, 23 nerve injuries were reported after surgical ligation and vein stripping (2.4 per cent across three studies). Twenty-one saphenous nerve injuries were reported by Canonico et al (2000); Michaels et al (2006) reported two cases of foot drop, commonly caused by nerve damage, both of which resolved completely.

Regarding paraesthesia, occurrence rates appeared greater after surgical ligation and stripping (117 cases, 8.6 per cent across eight studies) than after ELT (129 cases, 3.8 per cent across 19 studies), in line with the higher rate of nerve injury found after treatment with ligation and stripping.

Infection events

Comparative studies

Two of the five comparative studies reported infection as a complication of ELT or surgery (Appendix H). Rasmussen et al (2007) reported one patient (1.7 per cent) who suffered infection of their groin wound after surgery and was successfully treated with antibiotics. Vuylsteke et al (2006) reported one case (0.8 per cent) of a groin abscess in a

patient who underwent surgery, which required re-admission to hospital for incision and drainage followed by intravenous antibiotic treatment. No statistical comparisons were made between ELT and surgery regarding this complication.

All studies

Three cases of post-ELT infection were reported (0.3 per cent across seven studies); one patient of CEAP classification C6 in the study by Viarengo et al (2006) suffered an infection complication at the limb puncture site which required antibiotic therapy for 10 days. Puggioni et al (2005) found two patients suffered cellulitis, caused by bacterial infection of the connective tissue under the skin, but neither required hospitalisation.

A total of 63 post-operative infections after ligation and/or stripping were reported (2.4 per cent across 10 studies). Frings et al (2004) used ligation alone and reported one patient developed a significant groin wound infection post-procedure; the remaining 62 cases occurred after ligation and stripping. Three of the 63 were cases of cellulitis, reported in the studies by Michaels et al (2006) and Mofidi et al (2000). All infections resolved, though time periods for resolution were not provided. Treatments for infection varied; Kam et al (2003) and Vuylsteke et al (2006) treated infections with incision and drainage followed by antibiotics while Rasmussen et al used antibiotics without requiring hospital admission. Mofidi et al (2000) treated cellulitis conservatively while one of the affected patients in the study by Michaels et al (2006) required readmission and intravenous antibiotics.

Further to these events, eight cases of stitch sinus (5.1 per cent in one study) were reported after ligation and stripping. No information was provided regarding outcomes of these cases. Stitch sinus is not a potential outcome of ELT.

Bleeding complications

Comparative studies

None of the five comparative studies reported bleeding complications as an adverse event.

All studies

Five cases of significant bleeding complications were reported after ligation and stripping (0.6 per cent across two studies). Michaels et al (2006) reported that none of the three patients affected required transfusion, while Zbronski et al (2005) reported that the two patients affected required hospital admission for treatment of mild bleeding from the site of operation in the groin. No cases of significant bleeding complications were reported after use of ELT.

Haematoma, ecchymosis and bruising

Whilst all involve blood from ruptured capillaries collecting in surrounding tissue, haematomas, which in some circumstances require surgical drainage, are generally regarded as more serious than simple bruising or ecchymosis. However, it must be noted that explicit definitions of bruising, ecchymosis, and haematoma were not always available and the bruising complications of some patients may have been diagnosed differently by different researchers.

Comparative studies

Three of the five comparative studies reported on haematoma, bruising and ecchymosis (Appendix H). The study by de Medeiros (2006) reported all patients suffered some degree of haematoma, but significantly lower rates of large haematoma in patients who underwent ELT (20.0 per cent vs 60.0 per cent, P=0.03). Rasmussen et al (2007) reported no significant difference between treatments in occurrence rate of haematoma, while significantly fewer patients in the ELT group suffered bruising than those in the ligation and stripping group (11.3 per cent vs 25.4 per cent, P<0.05). Vuylsteke et al (2006) found four cases (3.1 per cent) of haematoma in the groin amongst the ligation and stripping patients, which were treated conservatively, but no cases of haematoma in ELT patients. The study also reported higher rates of bruising for ELT (50.0 per cent) and ligation and stripping (65.6 per cent) than was found by Rasmussen et al (2007); however, no statistical comparisons were made between the two treatments.

All studies

Occurrence rates of haematoma were greater after ligation and stripping (240 cases, 7.0 per cent across 10 studies) than after ELT (44 cases, 2.3 per cent across ten studies). In contrast, rates of bruising and ecchymosis were higher after ELT (1437 cases, 51.0 per cent across 16 studies) than after ligation and stripping (152 cases, 21.1 per cent across five studies). As previously mentioned, explicit definitions of bruising, ecchymosis, and haematoma were not always available. Thus, these discrepancies may possibly be due in part to differences in clinicians' definitions of significant bruising.

ELT-specific adverse events

Whilst occurrence rates for a number of adverse events appeared to be higher after ligation and stripping than ELT, there were a number of minor complications that occurred only after treatment with ELT; these included laser-related skin burn, induration along the treated vein, and a sensation of tightness along the treated limb.

Comparative studies

One of the five comparative studies reported ELT-specific adverse events (Appendix H); Vuylsteke et al (2006) reported 23 cases (19.5 per cent) of induration along the vein, which usually subsided after two weeks, and three cases (2.5 per cent) of second-degree laser skin burn, which healed completely without specific treatment.

All studies

Across all included studies, 19 cases of laser-related skin burn (0.5 per cent across 21 studies), 411 cases of induration (46.7 per cent across six studies) and 54 cases of a sensation of tightness along the treated limb (24.8 per cent across four studies) were reported; these relatively minor complications generally resolved spontaneously without specific treatment.

Other adverse events

Other adverse events of note include oedema, phlebitis, hyperpigmentation, lymphorrea and seroma; the rates of these adverse events (where reported) in the comparative studies are shown in Appendix H.

Comparative studies

The study by de Medeiros (2006) found significantly worse rates of oedema in surgery patients than ELT patients (40.0 per cent vs 15.0 per cent, *P*=0.02). Rasmussen et al (2007) reported two self-limiting cases of phlebitis in the both the ELT (3.2 per cent) and ligation and stripping (3.4 per cent) treatment groups; no significant difference between the treatment groups was found.

Wu et al (2005) defined minor complications as hyperpigmentation, numbness or loss of sensation, deep vein damage, thrombosis formation, neural injury, phlebitis or infection of incision location. The study did not report rates of each complication separately, instead reporting on the number of patients who suffered from at least one of these complications. Three ELT patients (15.0 per cent) and four ligation and stripping patients (13.3 per cent) suffered at least one minor complication; this was a non-significant difference.

All studies

Across all studies, occurrence rates of phlebitis appeared slightly higher after ELT (95 cases, 7.4 per cent across seven studies) than after surgical ligation and vein stripping (94 cases, 4.5 per cent across four studies). Rates of hyperpigmentation appeared similar between ELT (65 cases, 2.7 per cent across seven studies) and ligation and stripping (9 cases, 1.4 per cent across two studies). Occurrence of oedema seemed greater in ligation and stripping patients (8 cases, 40.0 per cent in one study) than in ELT patients (2 cases, 5.2 per cent across two studies); however, it should be noted that only two studies reported oedema as an adverse event and the reported occurrence rates came from a relatively small sample of patients.

Five cases of lymphorrhea and seroma were reported after treatment with ligation and stripping (0.5 per cent across three studies); Mofidi et al (2000) reported one case of lymph leak, which was treated conservatively, while Canonico et al (2000) found four patients developed post-treatment seroma successfully treated with medication. No cases of lymphorrhea or seroma were found in patients treated with ELT.

Post-procedural pain

It should be noted here that post-operative pain was recorded in a number of ways; definitions of post-operative pain varied from 'mild tenderness' to 'excessive pain'. Some studies asked patients to report their levels of pain on visual analogue scales, while others used analgesic usage.

Comparative studies

Post-operative pain was reported within all five comparative studies, but was reported in a variety of ways (Appendix H). Mekako et al (2006b) reported that three patients (4.8 per cent) in the surgery group required overnight admission to hospital immediately after the procedure for pain requiring parenteral analgesia, while no ELT patient required hospital admission. Regarding self-reported pain, de Medeiros (2006) queried patients 7 days post-treatment; no patients reported severe pain in either limb, and no significant difference in pain levels was reported between treatments. Rasmussen et al (2007) asked patients to record pain levels on a visual analogue scale from 0 to 10. Patients' results were plotted graphically, not numerically; thus, the results listed in Appendix H are approximations from selected time points. The study found patients who underwent

stripping reported significantly higher pain scores across the 10-day follow-up period than those who received ELT ($P<0.001$).

Regarding analgesic usage, Rasmussen et al (2007) reported no significant difference between treatment groups in the number of analgesic tablets required for the 10 days post-procedure. Vuylsteke et al (2006) reported that patients who underwent ELT required use of non-steroidal anti-inflammatory drugs (NSAIDs) for a significantly shorter period of time post-treatment than their ligation and stripping counterparts, in both unilaterally- (0.7 days vs 5.5 days, $P<0.001$) and bilaterally-treated patients (0.9 days vs 6.1 days, $P<0.001$). Wu et al (2005) reported that 23 patients (76.7 per cent) who had the saphenous vein stripped required post-operative analgesics, significantly more than the six ELT patients (30.0 per cent) requiring analgesics ($P<0.01$).

All studies

Post-procedural pain was found to be more frequent after ELT (533 cases, 25.6 per cent across 13 studies) than after ligation and stripping (70 cases, 7.1 per cent across five studies). This somewhat contradicts the findings of the comparative studies; however, as previously mentioned, post-operative pain was recorded in a number of ways. Thus, this discrepancy may possibly be due in part to differences between ELT and ligation and stripping studies in their definitions of post-operative pain.

Safety outcomes by ELT laser wavelength

To provide greater insight into the safety outcomes of ELT treatment, the adverse events reported for ELT in Table 14 were stratified by the wavelength of laser used, and are presented in Appendix H.

Few clear differences between wavelengths were evident in occurrence rate of adverse events, particularly amongst the more severe morbidities. Rates of thromboembolic complications, nerve injuries and infection appeared comparable across all wavelengths. The one study that reported on superficial thrombophlebitis after ELT using a 940 nm laser reported 10 cases (9.2 per cent in one study). Given that this was only reported by a single study and the overall sample size was relatively low, the significance of this finding should not be over-emphasised.

Some differences were evident amongst the minor complications; the most apparent was that after ELT using 940 nm or 1320 nm lasers, occurrence rates of post-procedural pain (77.5 per cent across three studies and 30.2 per cent across two studies respectively), bruising (77.5 per cent across two studies and 60.6 per cent in one study respectively) and induration (58.3 per cent across three studies and 45.5 per cent in one study respectively) were notably higher than after ELT with 810 nm or 980 nm lasers. It is important to note that all of these occurrence rates were the combined results of three studies by Proebstle et al (2003, 2005, 2006), with the exception of Goldman et al (2004) who reported no cases of post-operative pain after ELT of 22 patients with a 1320 nm laser. As has been previously mentioned, definitions of post-procedural pain and bruising differed somewhat between studies. When taken into consideration along with the differences in post-operative pain reported by Proebstle et al (2005) and Goldman et al (2004), it is possible that the higher reported occurrence rates may be due primarily to the particular clinical definitions of pain, bruising and induration chosen by Proebstle and colleagues. For example, Proebstle et al (2005) stated that pain was reported subjectively by patients within the following three classes: 'not present', 'present but no analgesics required', and 'present with analgesics necessary'. This definition differs from that used in

some studies, such as Puggioni et al (2005), who only reported patients who suffered from 'excessive pain'.

Summary of safety outcomes

Very few major complications or morbidities were reported for ELT or the comparative procedure of surgical ligation and vein stripping within the five comparative studies available. Those that were reported showed no substantial difference between treatment groups. Regarding minor morbidities and adverse events, few differences were found between ELT and surgical vein stripping in the comparative studies, though the differences that were found generally favoured the ELT procedure. Rasmussen et al (2007) found significantly lower post-procedural pain levels in ELT patients during 10 days of follow-up, while Vuylsteke et al (2006) and Wu et al (2005) found lower post-procedural anti-inflammatory and analgesic usage amongst ELT patients. The study by de Medeiros (2006) found lower haematoma and oedema occurrence among ELT patients while Rasmussen et al (2007) reported fewer ELT patients suffered post-procedural bruising.

When examining the complications and adverse events across all of the literature obtained, it is apparent that the ELT procedure carries with it a number of minor morbidities generally not found after surgical junction ligation and vein stripping, such as laser skin burn and induration. It also appears to have a slightly higher rate of incidence of some minor adverse events such as phlebitis. The results regarding bruising and post-procedural pain appear mixed, with studies directly comparing ELT to surgery showing ELT patients suffered less pain and bruising (Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005), while the incidence rates of the overall literature favour ligation and stripping; these findings should be interpreted carefully due to the variety of ways in which bruising and post-procedural pain were interpreted and reported. It is important to note that despite ELT carrying some distinct adverse events, the overall literature indicates that occurrence rates of more severe complications such as deep venous thrombosis, nerve injury and paraesthesia, post-operative infection and haematomas, appeared to be greater after ligation and stripping than after ELT.

Thus, it appears that the ELT procedure is at least as safe as the comparative procedure of conventional junction ligation and stripping.

Is it effective?

The primary clinical treatment outcome of ELT is the abolition of reflux in the saphenous vein, demonstrated by the complete occlusion or obliteration of the vein, and confirmed by Doppler and colour duplex ultrasound examination. Following the ELT procedure, reflux is assessed in the saphenous vein but not in other veins in the limb.

The main treatment outcome of the stripping procedure is the abolition of reflux achieved by the removal of the saphenous vein. Provided an adequate stripping procedure has been performed, reflux should not be present in the absent portion of the saphenous vein although it is possible for neovascularisation to occur along the tract. Follow-up studies should look for reflux or blood flow by colour duplex ultrasound examination in the treated section and in other veins in the limb.

Only studies that compared ELT with surgery were included to assess effectiveness outcomes. However, it should be noted that the differences in the methods of reporting outcomes of the two techniques render it difficult to compare their clinical outcomes in many studies.

Abolition of reflux

All five comparative studies provided clinical data regarding absence of reflux in limbs following ELT treatment (de Medeiros 2006; Mekako et al 2006b; Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005). At the end of follow-up, occlusion rates ranging from 94 to 96 per cent were reported (Table 15). Final reporting of outcomes ranged from a minimum of 12 weeks post-procedure by Mekako et al (2006b) to 12 months post-procedure in the study by Wu et al (2005). Three of the five studies provided comparable data for surgery (de Medeiros 2006; Rasmussen et al 2007; Wu et al 2005), reporting that between 94 and 100 per cent of limbs were free of reflux at final follow-up.

The study by de Medeiros (2006) reported that duplex ultrasound scan at 30-day follow-up showed that 19 limbs (95 per cent) treated with ELT were successfully occluded, while no reflux was reported in the 20 (100 per cent) surgically stripped limbs. No statistical comparison was made between ELT and surgery regarding absence of reflux.

Mekako et al (2006b) reported duplex ultrasound scans at 1- and 12-weeks post-procedure that showed GSV occlusion rates after ELT of 99 and 96 per cent respectively, and sapheno-femoral junction occlusion rates of 97 and 96 per cent respectively. No data were provided regarding reflux in limbs that had received surgery.

Rasmussen et al (2007) reported that occlusion rates after ELT were 100 per cent at 12 days and 1 month follow-up, 98 per cent at 3 months, and 94 per cent at 6 months. Two patients were lost to follow-up at 12 days, four at 1 month, six at 3 months, and 15 at 6 months. Absence of reflux in surgically stripped limbs was reported in 97 per cent of limbs at 12 days and 1 month, 100 per cent at 3 months, and 98 per cent at 6 months. The fluctuation in reflux rates is primarily due to patient attendance and losses to follow-up; two patients were lost to follow-up at 1 month, five at 3 months, and 18 at 6 months. Reflux was reported as present in two limbs due to the great saphenous vein breaking during the procedure and thus not being stripped successfully. These are classified as technical failures. Technical success or failure is not an effectiveness outcome for the purposes of the present study however these failures and consequent presence of reflux

should be noted. No statistical comparison was made between ELT and surgery regarding absence of reflux.

The study by Vuylsteke et al (2006) reported that 99 per cent of saphenous veins treated with ELT were occluded at 4-week follow-up, and 94 per cent of veins remained occluded at 9-month follow-up. Despite stating they experienced '100% success in removing the GSV by stripping' (Vuylsteke et al 2005, p.85), no data were provided regarding the presence or absence of reflux in the limbs that had been surgically stripped. Thus, while the rate of occlusion from ELT was comparable to the results of other studies, no comparison to surgery could be made.

Wu et al (2005) found that at the 12-month follow-up ultrasound examination, 95 per cent of limbs treated with ELT were reported to be free of reflux, compared to 94 per cent of limbs treated with surgical vein stripping; the difference in the absence of venous reflux between the two treatments was found to be non-significant.

Table 15 Post-treatment reflux outcomes – comparative studies

Study	Level of evidence	Length of follow-up		Outcome					
				Reflux-free limbs					
				12 days n (%)	1 month n (%)	3 months n (%)	6 months n (%)	9 months n (%)	12 months n (%)
de Medeiros (2006)	II	Mean: 26 months Range: 4.5-35.5	ELT (n=20)	-	19 (95)	-	-	-	-
			L/S (n=20)	-	20 (100)	-	-	-	-
			P value		-				
Mekako et al (2006b)	III-2	12 weeks	ELT (n=70)	69 (99)[a]	-	67 (96)	-	-	-
			L/S (n=62)	-	-	-	-	-	-
			P value						
Rasmussen et al (2007)	II	6 months	ELT (n=69)	67/67 (100)	65/65 (100)	62/63 (98)	51/54 (94)	-	-
			L/S (n=68)	66/68 (97)	64/66 (97)	63/63 (100)	49/50 (98)	-	-
			P value	-	-	-	-		
Vuylsteke et al (2006)	III-2	9 months	ELT (n=118)	-	117 (99)	-	-	111 (94)	-
			L/S (n=128)	-	-	-	-	-	-
			P value						
Wu et al (2005)	III-2	12 months	ELT (n=22)	-	-	-	-	-	21 (95)
			L/S (n=36)	-	-	-	-	-	34 (94)
			P value						NS

ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; –: Data not reported

[a] After 1-week follow-up

In summary, post-treatment reflux was similar for ELT and surgical ligation and vein stripping for all studies where reported as an outcome.

Recanalisation, neovascularisation and recurrence

Recanalisation is the spontaneous restoration of the lumen of the saphenous vein after occlusion by ELT has taken place. For the purposes of this review neovascularisation is the proliferation of blood vessels in tissue where the saphenous veins have been removed through the surgical ligation and stripping procedure. Neovascularisation is not necessarily clinically significant but may be a cosmetic issue for patients.

Three comparative studies explicitly reported on the recanalisation status of enrolled patients after ELT (Table 16). The studies by Vuylsteke et al (2006) (follow-up 9 months) and Rasmussen et al (2007) (follow-up 6 months) reported recanalisation rates after ELT of 5.9 per cent and 4.3 per cent respectively at the end of the follow-up period. Patients in the study by Vuylsteke et al (2006) were treated locally by means of foam sclerotherapy. The study by de Medeiros (2006) (mean follow-up 26 months), which used ligation in addition to ELT on the great saphenous vein, reported one case of recanalisation (5.0 per cent) 30 days post-treatment due to an insufficient perforator vein draining into the great saphenous vein. This patient received ligation of the perforator vein and at 24-month follow-up remained uneventful, although duplex ultrasound still detected the presence of reflux in the great saphenous vein. None of the comparative studies definitively reported occurrence of neovascularisation during follow-up; thus, a comparison of the two techniques with regards to recanalisation and neovascularisation could not be made.

Table 16 Recanalisation or recurrence outcomes – comparative studies

Study	Level of evidence	Length of follow-up		Outcome					
				Recanalisation / Recurrence					
				12 days n (%)	1 month n (%)	3 months n (%)	6 months n (%)	9 months n (%)	12 month n (%)
de Medeiros (2006)	II	Mean: 26 months Range: 4.5-35.5	ELT (n=20)	-	1 (5)	-	-	-	-
			L/S (n=20)	-	-	-	-	-	-
			P value						
Rasmussen et al (2007)	II	6 months	ELT (n=69)	0 (0)	0 (0)	1 (1)	3 (4)	-	-
			L/S (n=68)	-	-	-	-	-	-
			P value						
Vuylsteke et al (2006)	III-2	9 months	ELT (n=118)	-	-	-	-	7 (6)	-
			L/S (n=128)	-	-	-	-	-	-
			P value						
Wu et al (2005)	III-2	12 months	ELT (n=22)	-	-	-	-	-	1 (5)
			L/S (n=36)	-	-	-	-	-	2 (6)
			P value						NS

ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; –: Data not reported

It should be noted here that Wu et al (2005) reported 'recurrence rates' at 12 months post-treatment were 4.5 per cent after ELT and 5.6 per cent after surgical vein stripping (Table 16). While the translation of the study from Chinese to English made precise explanation difficult, 'recurrence' was roughly defined as the presence of ultrasound-documented blood flow or reflux in the region of the great saphenous vein, suggesting that revascularisation or neovascularisation may have occurred in those patients. There was no statistically significant difference between recurrence rates of the two treatments.

With limited comparative data available, no difference could be determined between ELT and ligation and stripping with regards to recanalisation, neovascularisation and recurrence.

Reduction of symptoms

Two comparative studies reported on the reduction of symptoms associated with varicose veins after ELT or surgical vein stripping (Table 17). The studies of Mekako et al (2006b) and Rasmussen et al (2007) reported the results of both the Aberdeen

Varicose Vein Questionnaire (AVVQ) and the Venous Clinical Severity Score (VCSS). The AVVQ is a validated 13-item instrument that covers all aspects of varicose vein clinical presentation (eg symptomatology, complications) and produces a disease-specific score from 0 (no venous symptoms) to 100 (extreme venous symptoms) (Garratt et al 1993). The VCSS is a validated measure of disease severity, combining nine clinical characteristics of venous disease (eg pain, inflammation) which are each scored from 0 to 3 (absent, mild, moderate, severe) plus a score of up to three points added for differences in background conservative therapy (compression and elevation) to produce a 30-point maximum flat scale (Kakkos et al 2003).

Table 17 Reduction of varicose symptoms – comparative studies

Study	Level of evidence	Length of follow-up	Time point		Outcome	
					AVVQ score (0 (no symptoms) – 100 (extreme symptoms))	VCSS score (0 (no symptoms) – 30 (extreme symptoms))
Mekako et al (2006b)[a]	III-2	12 weeks	Pre-treatment	ELT (n=70)	11.1 (8.9-17.4)	4 (3-5)
				L/S (n=62)	16.6 (12.6-20.6)	6 (4-8)
				P value	0.001	< 0.001
			1 week	ELT (n=70)	15.7 (12.6-22.3)	-
				L/S (n=62)	22 (18.1-26.7)	-
				P value	NS	
			6 weeks	ELT (n=70)	4.7	-
				L/S (n=62)	22 (18.1-26.7)	-
				P value	< 0.01	
			12 weeks	ELT (n=70)	0.6 (0-4.4)	0 (0-1)
				L/S (n=62)	4.4 (1.8-9.9)	0 (0-1)
				P value	< 0.01	NS
Rasmussen et al (2007)[b]	II	6 months	Pre-treatment	ELT (n=62)	18.6 (3.6-40.2)	2.8 (1-8)
				L/S (n=59)	16.1 (4.4-34.3)	2.4 (2-12)
				P value	NS	NS
			12 days	ELT (n=62)	23.1 (0-49.9)	-
				L/S (n=59)	21.5 (0-42.6)	-
				P value	NS	
			1 month	ELT (n=62)	14.2 (0-47.9)	-
				L/S (n=59)	13.7 (0-47.4)	-
				P value	NS	
			3 months	ELT (n=62)	6.9 (0-43.8)	0.1 (0-2)
				L/S (n=59)	8.2 (0-31.2)	0.2 (0-2)
				P value	NS	NS
			6 months	ELT (n=62)	7.1 (0-38.7)	0.4 (0-7)
				L/S (n=59)	5.3 (0-33.1)	0.2 (0-2)
				P value	NS	NS

AVVQ: Aberdeen varicose veins questionnaire; ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; VCSS: Venous clinical severity score; –: Data not reported
Values in bold type are significant differences

[a] Values for Mekako et al (2006b) are median (inter-quartile range)

[b] Values for Rasmussen et al (2007) are mean (range)

After adjusting for differences between ELT and surgery groups in baseline scores using ANCOVA, Mekako et al (2006b) found the ELT group demonstrated significantly better AVVQ scores than the surgical group at 6-week and 12-week follow-up. AVVQ scores for both ELT and surgery patient groups significantly deteriorated from baseline scores 1

week after treatment ($P<0.01$); however, from pre-treatment to 12-week follow-up there was a statistically significant 95 per cent improvement in AVVQ score in patients who underwent ELT ($P<0.001$) and a statistically significant 74 per cent improvement in surgical vein stripping patients ($P<0.001$). The study also found significant improvements in VCSS scores from pre-treatment to 12-week follow-up in both the ELT ($P<0.001$) and surgical vein stripping ($P<0.001$) groups; however inter-group analysis demonstrated no significant difference between the ELT and ligation and stripping procedures in VCSS score.

Rasmussen et al (2007) also noted a clear deterioration in AVVQ scores in both treatment groups after 12 days of follow-up. However, scores in both treatment groups had significantly improved from pre-treatment by 3-month follow-up ($P<0.05$). No significant difference in AVVQ scores was found between ELT and surgical vein stripping. Mean VCSS scores improved significantly by 3-month follow-up ($P<0.05$) within both treatment groups, but no significant differences were found between ELT and stripping at any time point.

In general, ELT appeared to be at least as, or slightly more, effective in reducing varicose vein symptoms than surgical ligation and stripping. It is worth noting that baseline AVVQ and VCSS scores appeared quite low in both studies; however, both scales are designed to assess the severity of a wide range of varicose veins, including those with healed or active ulceration. The low baseline AVVQ and VCSS scores may be due in part to study selection criteria. For example, the study of Rasmussen et al (2007) imposed stringent selection criteria to exclude patients with the severe or complicated varicose veins and patients with healed or active venous ulceration, restricting treatment to patients with relatively simple varicosities (CEAP classification C2-C4). While Mekako et al (2006b) did not provide explicit inclusion and exclusion criteria, they treated only three patients of CEAP classification C5 (healed ulceration), and it is quite possible they too restricted themselves to treating simpler varicose veins.

Quality of life

Three of the five comparative studies reported on the quality of life of patients after ELT or surgical vein stripping.

Short Form-36

The studies of Mekako et al (2006b) and Rasmussen et al (2007) reported pre- and post-treatment scores of the Short Form-36 (SF-36) health survey, a valid and reliable measure of health status and quality of life (Smith et al 1999). These scores are presented in Appendix H. The SF-36 consists of 36 items aggregated to form eight domains, each of which is scored from 0 (lowest quality of life) to 100 (highest quality of life).

After adjusting for baseline differences between ELT and stripping groups using ANCOVA, Mekako et al (2006b) found the ELT group demonstrated significantly better SF-36 scores in the domains of physical functioning, role-physical, bodily pain and social functioning at 1-week follow-up ($P<0.01$). At 6-week follow-up scores for the physical functioning and role-physical domains remained significantly better for ELT patients ($P<0.01$); however, at the end of follow-up (12 weeks) there were no significant differences between the treatment groups. There was a statistically significant deterioration 1-week post-treatment in patients who underwent surgical vein stripping in the domains of physical function, role-physical, bodily pain and social functioning ($P<0.01$). By the completion of follow-up, however, these four domain scores had

significantly improved from baseline levels, along with the domain scores of vitality and mental health ($P<0.01$). There was no immediate deterioration in ELT patients, and by the end of the follow-up period there had been significant improvement in the physical function, role-physical, bodily pain, general health, vitality and social functioning domains ($P<0.01$).

Rasmussen et al (2007) reported clear deterioration after 12 days in the domains of physical functioning, role-physical and bodily pain within both treatment groups. However, from baseline to 3-month follow-up both treatment groups significantly improved in the physical functioning, role-physical, bodily pain, vitality, social functioning and role-emotional domains ($P<0.0001$). One difference that just reached significance was noted between treatment groups, with patients who underwent ELT scoring lower on the bodily pain domain at 12-day follow-up than patients who underwent stripping ($P=0.042$).

Chronic Venous Insufficiency Quality of Life Questionnaire

The study by Vuylsteke et al (2006) reported results from the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) (Table 18). The CIVIQ is a validated and reliable 20-item questionnaire, providing a profile on four quality of life dimensions specific to venous derangement of the lower limb (Launois et al 1996). Questionnaire items are scored on a 5-point ordinal scale, with the total score a global index of quality of life ranked from 0 (highest quality of life) to 100 (lowest quality of life). The researchers analysed the results for unilaterally- and bilaterally-treated patients separately. Patients who received ELT reported significantly higher quality of life at 4-week follow-up than patients who underwent stripping, in both unilaterally- ($P<0.001$) and bilaterally-treated ($P=0.002$) patient groups.

Table 18 Quality of life (CIVIQ) outcomes – comparative studies

Study	Level of evidence	Length of follow-up		Outcome	
				Mean CIVIQ scores at 4-week follow-up (0 (highest quality of life) – 100 (lowest quality of life))	
				Unilaterally-treated patients (ELT: n=42; L/S: n=40)	Bilaterally-treated patients (ELT: n=38; L/S: n=44)
Vuylsteke et al (2006)	III-2	9 months	ELT (n=80)	23.7 ± 3.7	28.6 ± 6.3
			L/S (n=84)	35.4 ± 12.0	36.4 ± 10.8
			P value	< 0.001	0.002

CIVIQ: Chronic venous insufficiency quality of life questionnaire; ELT: Endovenous laser therapy; L/S: Ligation/stripping
Plus-minus values are mean ± standard deviation; values in bold type are significant differences

In summary, ELT appeared to produce equal or slightly improved quality of life scores compared to surgical ligation and vein stripping.

Time taken to resume normal activities

Two comparative studies (Rasmussen et al 2007; Vuylsteke et al 2006) reported on the time taken for patients to return to normal activities or work after ELT or surgical vein stripping (Table 19). Both studies advised patients to resume normal activities as soon as possible after treatment. Rasmussen et al (2007) reported both time to resume normal activity and time to resume work, but found no significant difference between treatment groups for either outcome. Vuylsteke et al (2006) recorded time to resume work, measured in days of sick leave as controlled by the patient's general practitioner, separately for unilaterally- and bilaterally-treated patients. The study reported patients

receiving ELT, both unilaterally and bilaterally, required significantly fewer sick leave days than their counterparts who underwent stripping ($P<0.001$ for both treatment groups). It should be noted here that Vuylsteke et al (2006) restricted their study population to patients working full-time, while Rasmussen et al. (2007) made no such restrictions.

Table 19 Time required for resumption of normal activities post-treatment

Study	Level of evidence	Length of follow-up		Outcome	
				Mean time to resume normal activity (range) in days	Mean time to resume work (range) in days
Rasmussen et al (2007)	II	6 months	ELT (n=62)	6.9 ± 7.0 (0-29)	7.0 ± 6.0 (1-31)
			L/S (n=59)	7.7 ± 6.1 (0-29)	7.6 ± 4.9 (1-28)
			P value	NS	NS
Vuylsteke et al (2006)	III-2	9 months	ELT (unilateral) (n=42)	-	4.1 ± 4.2
			L/S (unilateral) (n=40)	-	18.86 ± 14.5
			P value		< 0.001
			ELT (bilateral) (n=38)	-	8.64 ± 8.5
			L/S (bilateral) (n=44)	-	22.43 ± 13.8
			P value		< 0.001

ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; –: Data not reported
Plus-minus values are mean ± standard deviation; values in bold type are significant differences

From the two studies available, ELT patients appeared to be able to return to normal activity just as soon, or sooner, than ligation and stripping patients.

Operating time for procedure

Only one study compared the length of operating time for the ELT procedure to that of the stripping procedure (Table 20). Wu et al (2005) reported that the ELT procedure had a mean procedure time of 28.5 minutes, significantly faster than the 41.1 minutes required for stripping ($P<0.01$). Tributary vessels were treated during ELT, and are commonly treated during conventional surgery on the saphenous vein.

Table 20 Operating time for procedure

Study	Level of evidence	Length of follow-up		Outcome
				Mean operating time (range) in minutes
Wu et al (2005)	III-2	12 months	ELT (n=20)	28.54 ± 7.20 (18-45)
			L/S (n=30)	41.14 ± 8.80 (27-65)
			P value	< 0.01

ELT: Endovenous laser therapy; L/S: Ligation/stripping
Plus-minus values are mean ± standard deviation; values in bold type are significant differences

Summary of effectiveness outcomes

Few differences in clinical effectiveness outcomes were found between ELT and the comparative procedure of surgical ligation and vein stripping. It was not possible to make comparisons for the majority of studies, as clinical outcomes of surgical vein stripping were generally reported poorly or not at all. This difficulty was compounded by the different aims of ELT and stripping in respect to reflux. However, those studies that reported clinical outcomes for both techniques found little difference between the techniques. Neither de Medeiros (2006) nor Rasmussen et al (2007) reported any notable difference in venous occlusion rates, and Wu et al (2005) found no significant difference in rates of recurrence of blood flow or reflux after 12-month follow-up. Thus, it appears that ELT is an effective treatment for occluding the saphenous vein, and is at least as effective as the conventional surgical procedure.

A number of differences were found between the treatments with regards to non-clinical effectiveness outcomes. Mekako et al (2006b) and Rasmussen et al (2007) both found that ELT and surgical vein stripping had significantly reduced symptoms of varicose veins by the completion of follow-up. Mekako et al (2006b) also found that ELT patients reported fewer symptoms than ligation and stripping patients at 6- and 12-week follow-up; however, this may be confounded by the fact that ELT patients reported significantly better scores at baseline. Mekako et al (2006b) and Rasmussen et al (2007) found at the end of the follow-up period quality of life scores had significantly improved after ELT and ligation and stripping; both studies also found that patients who underwent ELT reported better quality of life scores in the short term, but no differences between ELT and ligation and stripping by the completion of follow-up. Vuylsteke et al (2006) found patients who received ELT, both unilaterally and bilaterally, reported better quality of life results and took less time to return to work than patients who had undergone ligation and stripping. Wu et al (2005) reported operating time for ELT was significantly shorter than for surgical vein stripping.

In summary, ELT appears to be potentially more effective in the short term, and at least as effective overall, as the comparative procedure of junction ligation and vein stripping for the treatment of varicose veins.

What are the economic considerations?

Economic evaluation of new healthcare technologies is important when determining whether the new initiative offered additional benefits and at what cost. Economic evaluations are able to determine whether the new initiative is dominated by (or dominates) the existing technology, such that the costs are higher (lower) and the effectiveness is less (greater). Economic evaluation is particularly important if the new initiative offers health benefits at additional costs. Within a constrained healthcare budget, determining the additional cost that would be paid for a given health gain is important in order to ascertain whether such incremental costs represent value for money.

The usual process for an economic evaluation is: first, to determine the incremental effectiveness, which is the additional benefit associated with the new technology relative to current practice; second, to determine the incremental costs, which is the difference in costs between the new initiative and current practice; and, finally, to calculate the incremental cost-effectiveness ratio (ICER) using the following ratio:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiveness_{New} - Effectiveness_{Comparator}}$$

Restrictions of the economic evaluation

It was decided by the advisory panel that the economic evaluation of ELT would be limited to a cost analysis, since there is insufficient evidence to support superior effectiveness for either ELT or the comparator.

Search strategies

As described in the 'approach to assessment', a search strategy was developed to systematically identify studies in which ELT was used for the treatment of varicose veins.

Databases of peer-reviewed literature including Medline, PubMed, CINAHL and Cochrane have been searched. The bibliographies of all retrieved publications were hand-searched for any relevant references missing in the database search. Web-based searches included the Internet engines 'Google' and 'Google scholar'.

In addition to the search terms described in the 'approach to assessment' section, Cost$ or Econ$ were added. This was to identify any published cost-effectiveness analysis. The inclusion and exclusion criteria remained the same.

Background

Four studies comparing ELT for the treatment of varicose veins to surgical vein stripping with respect to clinical outcomes were identified through the systematic literature review (de Medeiros 2006; Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005). Two of the studies include a cost-effectiveness component to their analysis. These studies will be briefly reviewed below. For the purpose of this cost analysis, the effectiveness data is extracted from the aforementioned studies and cost parameters are estimated using current Australian data.

Rationale for the cost analysis

It was decided by the advisory panel that the abolition of reflux in the saphenous vein, demonstrated by the complete occlusion or obliteration of the vein and confirmed by Doppler and colour duplex ultrasound examination, was the primary clinical endpoint, and surgical junction ligation and vein stripping would be the comparator for the cost analysis.

As previously discussed, no significant differences in the primary outcome were demonstrated between the two treatment options. Consequently, until more data are published supporting the superior effectiveness of either ELT or surgical vein stripping for the ablation of saphenous vein reflux, a cost-effectiveness analysis is not warranted. Therefore, the aim of the present economic evaluation will be to review the costs of ELT compared to surgical vein stripping for the treatment of patients with varicose veins when these interventions are provided under Australian conditions, and to provide an indication of the extent of uncertainty.

Assumptions

- The abolition of reflux in the saphenous vein, demonstrated by the complete occlusion or obliteration of the vein, was the primary clinical endpoint.
- Effectiveness data with respect to clinical outcomes is obtained from four studies comparing ELT with surgical vein stripping (de Medeiros 2006; Rasmussen et al 2007; Vuylsteke et al 2006; Wu et al 2005).
- It is assumed that the primary outcomes between studies are comparable.
- The cost analysis is restricted to primary varicose veins in unilaterally affected legs. The cost of varicose veins in bilaterally affected legs has been ignored.
- Only incremental costs are calculated. Therefore costs constant between treatment groups (as advised by expert opinion), such as medication and compression stockings, have been excluded.
- The perspective of the cost analysis is limited to the costs faced by the healthcare system for the base case. Cost of patient time is included in the sensitivity analysis.
- A discount rate of 5 per cent per annum was applied to all costs.

Evidence of cost-effectiveness

The original MSAC report of endovascular laser treatment of varicose veins (MSAC 2003) found insufficient evidence pertaining to the effectiveness of ELT. Consequently the cost-effectiveness of ELT in comparison with junction ligation and vein stripping was not calculated. Two recent studies comparing ELT to surgical ligation and stripping for the treatment of varicose veins have included a cost-effectiveness component to their analysis (Vuylsteke et al 2006; Rasmussen et al 2007).

Vuylsteke et al (2006) reported on the comparative costs of ELT for treatment of varicose veins with the conventional ligation and stripping operation. One hundred and sixty four patients with varicose veins were assigned to ELT (n=80, 118 legs) or ligation and stripping (n=84, 124 legs). The study population was limited to full-time working patients. The comparison of costs included both direct medical costs and costs resulting from lost productivity of the patient. The study demonstrated less post-operative complications in the ELT group and a reduction in the number of required sick leave days (18.9 compared to 4.1 in the unilateral cohort). The direct treatment costs were

higher in the ELT group (€853 compared to € 716). However, once productivity was accounted for, the costs of the ELT group were significantly lower (€1277 compared to €2659). The authors concluded that ELT offers 'shorter sick leave and faster return to usual occupation, and it appears to be cost-saving for society'. As the study was limited to only full-time working patients, the generalisability of the results to older patients is questionable. Additionally, by measuring the productivity costs of working patients, the assumption of cost-effectiveness will be reduced with the treatment of non-working individuals.

Rasmussen et al (2007) also compared ELT to surgical ligation and stripping. One hundred and twenty one patients with varicose veins were assigned to ELT (n=62, 69 legs) or ligation and stripping (n=59, 68 legs). This study was not restricted to working individuals. The direct treatment costs were high in the ELT group (€1391 compared to €924); the additional cost was associated with the capital costs of the ELT equipment and the extra duplex imaging. The time to resume work in this study was 7 days in the ELT group and 7.6 days in the surgical group. Taking this into account, the total estimated cost of ELT was €3396 compared with €3085 in the control group. However, the authors do not explain how they calculated the productivity costs.

Estimates of costs

Average capital costs per procedure

Average capital costs per procedure are based on estimates of the purchase price of equipment, life of equipment, maintenance and number of procedures performed per annum. These estimates were provided by the applicant or determined from expert opinion (Table 21). The opportunity cost of capital was included with the forgone capital return calculated using a 5 per cent discount rate. The values are sensitive to the number of procedures per annum.

For the basis of the analysis, average capital costs for ELT are estimated based upon the average number of procedures (75 per annum) over the estimated lifetime of the machine ($128 per procedure). For the sensitivity analysis, the lower estimate is $83 per procedure based upon 100 procedures per annum over 10 years and the upper estimate is $238 per procedure based upon 50 procedures per annum over 6 years.

Table 21 Calculation of average capital costs per procedure for ELT

Item	Cost ($AU)	Cost + GST ($AU)	Life in years (range)	Annual cost / machine ($AU) (range)
Purchase price of ELT	$50,000	$55,000	8[a] (6 - 10 years)	$6,875 (5,500 – 9,167)
Foregone capital return		5% of $55,000	Annual	$2,750
Maintenance	Annual maintenance charge $0 per year[b]			$0
Total opportunity cost of capital				$9,625 (8,250 – 11,917)
Average cost based on estimated procedures/machine/year[c]			50 75 100	$193 (165 – 238) $128 (110 – 159) $96 (83 – 119)

[a] Estimated life of laser provided by Applicant

[b] Maintenance cost provided by Applicant

[c] Estimated procedures per year

Cost-analysis

The cost analysis of the base case scenario is to determine the incremental cost, that is, the change in cost per patient for receiving ELT rather than ligation and stripping. Based upon no difference in clinical effectiveness outcomes, the analysis demonstrates that the incremental cost per patient of receiving ELT rather than surgical junction ligation and vein stripping for varicose veins is -$171, in other words a cost saving (Table 22). The bulk of the additional cost of ELT is associated with: the higher estimated procedural fee ($606 versus $481.85); the additional capital cost of buying the ELT equipment and consumables ($128 + $600 + $50); and the duplex imaging ($111.05). These costs are offset by reduced staffing costs and a saving in the cost of day surgery, as opposed to hospitalisation ($1500 versus $2500, including hire of the theatre, nursing staff and consumables).

The cost of sclerotherapy after ELT or ligation and stripping also adds to the incremental cost of ELT. It is estimated (as advised by expert clinical opinion) that the average patient will require 1.5 sessions of sclerotherapy post-ELT compared to an average of 0.2 sclerotherapy sessions post-ligation and stripping.

Table 22 Average incremental costs per patient of performing ELT (base case)

Consumables	Surgical vein stripping		ELT		Incremental cost of ELT patient ($AU)
	Units / patient	Cost ($AU)	Units / patient	Cost ($AU)	
Fixed cost					
Theatre facilities fees + nursing staff + 1 night hospitalisation[a]	1	$2,500.00	0		
Day theatre + nursing staff	0		1	$1,500.00	-$1,000.00
Consumables					
Laser fibre	0	$0	1	$600	
Catheters + introducers	0	$0	1	$50	
Vein stripper[b]	1	$24.07	0	$0	$625.93
Procedure (ELT or HP)					
MBS 32508	1	$481.85			
Proposed fee[c]			1	$606.00	
Anaesthetic	1	$192.74	0	$0	
Assistant	1	$96.37	0	$0	-$164.96
Duplex					
MBS 55296	0	$0	1	$111.05	$111.05
Capital cost (including opportunity cost)	0	$0	1	$128.00	$128.00
Additional treatment[d]					
Sclerotherapy MBS 32501	0.2	$99.15	1.5	$99.15	$128.90
Incremental cost ELT per patient					-$170.75

[a] Figure based on expert advice

[b] Figure from Astra tech

[c] Figure from Applicant

[d] Number of sclerotherapy sessions as estimated by expert advice

Sensitivity analysis

There is a degree of certainty regarding the costs of the surgical vein stripping procedure. Therefore the main uncertainty, and apparent driver of the incremental cost per patient, is the capital cost of buying the ELT equipment ($128) and the laser fibre ($600). The cost of capital equipment is based on an estimated 75 procedures per year over a lifetime of 8 years (Applicant estimate). Consequently if more procedures and/or the lifetime of the equipment are longer the capital costs will be reduced. For example, the capital cost is $83 per procedure based upon 100 procedures per annum over 10 years. The converse is also true; for example, the capital cost is $238 per procedure based upon 50 procedures per annum over 6 years.

The proposed MBS fee for ELT is higher than the current MBS fee for surgical vein stripping (MBS 32508 = $481.85, versus proposed ELT fee = $606). The proposed fee was provided by the Applicant, based on the additional training and skills required to perform ELT. It is worth noting that were the current MBS fee and proposed fee similar, this would reflect in an increased cost saving per ELT procedure. For example, if the proposed fee equalled the current MBS 32508 fee, the cost saving per ELT procedure would be $294.90, as opposed to $170.75 with the differential fee.

In the base case the cost of the laser fibre is based on a single use device. However, there are multiple-use alternatives available. By using a multi-use laser fibre the cost of consumables could be reduced to $300 per patient (including the additional cost of catheters, cleaning and sterilisation). However, clinicians and patients may prefer to use a single-use fibre.

Discussion

Compared to surgical vein stripping, ELT has been reported to be associated with a lower complication rate, higher patient preference, reduced short-term post-operative pain, shorter sick leave and a faster resumption of normal activities.

The use of productivity in economic analysis has been considered controversial for a number of reasons. Firstly, it is methodologically challenging to accurately measure the effect that an additional day off of work costs society. Secondly, there are concerns about equity, since illness in people of working age will be valued more highly than illness in the elderly. With these restrictions in mind, productivity was excluded from this report.

Cost-effectiveness

The cost-effectiveness analysis was derived from the clinical effectiveness data previously described. This showed ELT appears at least as effective as the comparator, with potentially reduced short-term postoperative pain and faster resumption of normal activities.

A cost-analysis was conducted based on the assumption of no significant differences between treatments in primary clinical outcomes. It is also based on the estimate that receiving ELT rather than surgical vein stripping for the treatment of unilateral varicose veins is associated with a modest cost saving (estimated incremental cost per patient = -$171), despite ELT being associated with the higher procedural fee, capital cost of the ELT equipment, duplex ultrasound, additional sclerotherapy and disposable laser fibre and catheters. These costs are offset by reduced staffing costs and a saving in the cost of day surgery, as opposed to hospitalisation.

Impact of ELT on the Australian healthcare system

A further point of concern centres on the potential for the new initiative to increase demand for treatment due to additional and perceived health benefits, and the wider availability of a less invasive technology. Although there is insufficient evidence to support superior clinical effectiveness in reducing symptoms for either ELT or the comparator, benefits such as use of local instead of general anaesthetic, shorter operating time and faster recovery suggest a potential increase in demand for ELT treatment if it were to be made available under the MBS. In addition, a number of individuals that currently opt to be treated with ELT as private patients would also be eligible for ELT under the MBS. As such, determining the potential impact of ELT on the Australian healthcare system becomes important.

One concern might be the increased treatment of varicose veins with ELT for cosmetic rather than medical reasons; however, clinical opinion suggests this ought to be minimal as the varicose vein has to be symptomatic and large. As a catheter must be inserted into the lumen of the vein to be treated, ELT can only be performed on large veins. Expert clinical opinion suggests that ELT is not viable on saphenous veins smaller than 4.5 mm in diameter, and cannot be used for the treatment of small veins or telangiectases.

The exact prevalence of varicose veins within the Australian population remains difficult to determine. Estimates from the AIHW suggest approximately 440,000 Australians suffer from varicose veins as a long-term condition (AIHW 2004); however, it is unknown how many of these meet physiological requirements for ELT and would seek treatment if it became available under the MBS. When estimating the number of patients who may seek ELT, it must first be noted that from the introduction of ELT technology to Australia in early 2002 to December 2006, ELT procedures were claimed erroneously under MBS item 35321. During this period claims for varicose surgery (MBS items 32508 and 32511) fell by 2,927 while claims for MBS item 35321 rose by 2,464[1], the assumption being that ELT was replacing surgery without a significant increase in overall demand for treatment (actual reduction in procedures of 463). In December 2006 ELT was specifically restricted from all MBS items.

Estimation of the potential increase in costs of treating varicose veins

Due to these uncertainties, a sensitivity analysis of financial impact was performed based on MBS data and expert clinical opinion. Potential increase in demand for varicose vein treatment upon funding of ELT was estimated to range between 0 and 100 per cent above current numbers. The lower bound of 0 per cent was based on the assumption that ELT would directly replace surgery. However, the advisory panel and clinicians agreed that some increase in demand would be likely, especially in the initial period after ELT becomes MBS funded, as patients who would otherwise avoid surgery seek legitimate treatment for their condition. The upper bound of a 100 per cent increase was based on a potential worst-case scenario. Clinical experts within the advisory panel were of the opinion that after addition of ELT to the MBS, demand for varicose vein treatment would increase to approximately 50 per cent above current levels in the first year, decreasing to 25 per cent above current levels in the second year and 10 per cent above current levels in the third year, with demand stabilising after that period.

The current number of patients receiving treatment for varicose veins was determined from the MBS claims database.[2] Between July 2006 and June 2007, 7,425 and 910 patients received surgical treatment for varicose veins under MBS items 32508 and 32511 respectively, while 3,667 patients underwent treatment with MBS item 35321, a combined total of 12,002 patients.

Calculated from figures shown in Table 22, if all 12,002 patients were to receive ELT instead of ligation and stripping, the additional saving to the healthcare system would be ($1,423,000). As previously discussed, there is the possibility that the introduction of ELT may increase the demand for varicose vein treatment. Estimates of the additional cost to the healthcare system for the treatment of an increased number of patients, assuming all patients receive ELT, are presented in Table 23.

[1] Retrieved January 31, 2008 from http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

[2] Retrieved August 29, 2007 from http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Table 23 Estimated additional costs due to increase in treatment demand for one year only

Increase in varicose veins treated (%)	Total number of patients treated	Cost to health service (A$)	Additional cost (A$)
0	12002	$37,736,000	-
10	13202	$41,509,000	$3,774,000
25	15003	$47,169,000	$9,434,000
50	18003	$56,603,000	$18,868,000
100	24004	$75,471,000	$37,756,000

What are the consumer considerations?

As part of this review, the advisory panel deemed it important to obtain consumer opinion regarding the ELT procedure. To this end a small consumer group, predominantly female and currently in the workforce, was approached. The information and opinion provided by this group generally favoured the ELT procedure for a number of reasons. These included cosmetic effectiveness (ie minimal visible scarring), reduction of pain and relief of varicose symptoms, thus allowing them to maintain physical activities with minimal interruption and return to the workplace sooner. They also appreciated that as an outpatient procedure, ELT provided them with a scheduled and planned approach, allowed for budget planning and avoided the uncertainty of waiting lists associated with inpatient procedures.

Conclusions

In 2003, MSAC reviewed the evidence associated with ELT for the treatment of varicose veins. Based on the absence of controlled trials directly comparing ELT to surgery at the time of that review, no definitive statement of effectiveness or cost-effectiveness of the procedures could be made. The systematic literature search of the current review revealed a total of five studies that directly compared the use of ELT to conventional junction ligation and vein stripping for the treatment of varicose veins, two of which were RCTs; the availability of these studies allowed the comparative safety, effectiveness and cost-effectiveness of ELT and ligation and stripping to be assessed.

Safety

Three of the five comparative studies reported safety outcomes and adverse events clearly and stratified by treatment group. Mekako et al (2006b) reported adverse events in very little detail and Wu et al (2005) did not provide incidence rates of individual complications. Very few major complications or morbidities were reported for ELT or the comparative procedure of surgical ligation and vein stripping within these studies; where they were reported, no substantial difference in occurrence was found between treatments. Few significant differences in minor morbidities and adverse events were found between ELT and surgery, while the differences that were found generally favoured the ELT procedure. The study by de Medeiros (2006) found lower haematoma and oedema occurrence among ELT patients. Rasmussen et al (2007) reported significantly fewer ELT patients suffered bruising, and significantly lower pain levels in ELT patients at follow-up. Vuylsteke et al (2006) and Wu et al (2005) both found lower post-procedural anti-inflammatory and analgesic requirements amongst ELT patients.

Across all studies, ecchymosis and bruising, induration, a sensation of tightness in the limb and post-operative pain were common adverse events associated with ELT. In the majority of cases these symptoms were self-limiting or only required treatment with mild medication. Ecchymosis or bruising was the most common adverse event with an occurrence rate of 51.0 per cent, and was reported in 16 of the 40 ELT studies. The most potentially serious adverse events reported related to post-treatment formation of emboli or thromboses and nerve damage. Pulmonary embolism occurred in only one patient, who experienced no long-term consequences (Myers et al 2006). Twenty cases of deep venous thrombosis (0.4 per cent of reported limbs) were identified across all ELT-treated patients; the majority of thromboses resolved spontaneously without further treatment. Seventeen cases of nerve injury were reported after ELT (0.8 per cent of reported limbs); after-effects of two cases of neuritis persisted from 4 to 8 months, one case of sural nerve palsy resolved after 6 months, and one case of saphenous nerve damage had not resolved after 12 months.

Ecchymosis and bruising, paraesthesia, haematoma and post-procedural pain were common adverse events associated with the 'gold standard' of surgical ligation and stripping. While these events are usually self-limiting, as a form of nerve injury paraesthesia can persist over an extended period of time, while haematoma may on occasion require surgical drainage for resolution. Ecchymosis or bruising was the most common adverse event with an occurrence rate of 21.1 per cent, and was reported in five of the 22 ligation and stripping studies. Thirty cases of deep venous thrombosis were reported after ligation and stripping (1.5 per cent of reported limbs); rates of resolution

were generally not reported. A total of 23 nerve injuries were reported after surgical ligation and vein stripping (2.4 per cent of reported limbs); rates of resolution were generally not reported.

It should be noted here that risks to patient safety may be greater when surgically stripping the small saphenous vein. This procedure is avoided by the majority of surgeons primarily due to fear of nerve damage (Winterborn et al 2004); as such, there are relatively few publications that examine the outcomes of stripping of the small saphenous vein. This review included only one such study (Michaels et al 2006), which reported the occurrence of two nerve injuries; however, it was not reported how many patients received small saphenous stripping, nor whether the nerve injuries were due to stripping of the small saphenous vein. Ten ELT studies reported on ablation of the small saphenous vein; one nerve injury (0.25 per cent of reported limbs) was reported in one study (Myers et al 2006) while six cases of paraesthesia (2.2 per cent of reported limbs) were found across two studies (Gibson et al 2007; Theivacumar et al 2007). These findings are inconclusive; however, it appears ELT is no less safe than surgical vein stripping for treatment of small saphenous vein reflux.

The ELT procedure entails some minor adverse events distinct from ligation and stripping, such as laser skin burn and induration. It also appears to have a slightly higher incidence of some minor adverse events such as phlebitis. The results regarding bruising and post-procedural pain appear mixed and should be interpreted carefully due to the variety of ways in which bruising and pain were defined across studies. Overall, the literature indicates that occurrence rates of more serious complications such as deep venous thrombosis, nerve injury and paraesthesia, post-operative infection and haematomas appeared to be higher after ligation and stripping than after ELT.

From the available literature it appears that the ELT procedure is at least as safe as the comparative procedure of conventional junction ligation and vein stripping.

Effectiveness

Only studies that directly compared ELT with surgical vein stripping were included to assess effectiveness outcomes. The primary clinical treatment outcome of ELT is the abolition of reflux in the saphenous vein, while for vein stripping it is the abolition of reflux achieved by the removal of the saphenous vein. Comparisons were not possible for the majority of studies, as clinical outcomes of surgical vein stripping were reported poorly or not at all; Mekako et al (2006b) did not report clinical outcomes stratified by treatment, and Vuylsteke et al (2006) did not report clinical outcomes for ligation and stripping. The difficulty of making comparisons was compounded by the different aims of ELT and stripping in respect to reflux. Given the dynamic nature of the condition, a follow-up of 6 to 12 months is adequate to determine effectiveness of treatment in a particular area of the limb. Three of the five comparative studies provided follow-up data of 6 months or more on the absence of reflux in treated limbs, while the longest follow-up was 12 months.

Of the five comparative studies, four provided clinical data regarding absence of reflux in limbs following ELT; at the conclusion of follow-up, reflux was absent in 94.1 to 95.5 per cent of limbs. The study with the longest follow-up (12 months) reported 95.5 per cent of limbs remained free of blood flow or reflux. The combination of ELT and ligation of the great saphenous vein resulted in 95.0 per cent of limbs remaining reflux-free after 1-month follow-up (de Medeiros 2006). Three studies provided clinical data

regarding absence of reflux in limbs following ligation and stripping; at the conclusion of follow-up, reflux was absent in 94.4 to 100.0 per cent of limbs. The study with the longest follow-up (12 months) reported 94.4 per cent of limbs remained free of blood flow or reflux.

The three studies that reported clinical outcomes for ELT and ligation and stripping found little difference between the procedures. Neither de Medeiros (2006) nor Rasmussen et al (2007) reported any notable difference in rates of abolition of reflux, and Wu et al (2005) found no significant difference in rates of recurrence of blood flow or reflux at 12-month follow-up. It appears that ELT is an effective treatment for occluding the saphenous vein, and is at least as effective as the conventional stripping procedure.

More differences were found between ELT and ligation and stripping with respect to non-clinical effectiveness outcomes. Mekako et al (2006b) found that ELT patients reported fewer symptoms of varicose veins than ligation and stripping patients at 6- and 12-week follow-up, and better scores on a number of quality of life domains at 1- and 6-week follow-up; however, these findings may be confounded by the fact that ELT patients also reported significantly better scores at baseline. Rasmussen et al (2007) reported one difference in quality of life scores that just reached statistical significance, with ELT patients reporting less bodily pain after 12 days of follow-up. Both studies found no differences between ELT and ligation and stripping in quality of life scores by the completion of follow-up. Vuylsteke et al (2006) found patients who received ELT, both unilaterally and bilaterally, reported better quality of life results and took less time to return to work than patients who had undergone stripping, while Wu et al (2005) reported mean operating time for ELT was significantly shorter than for surgical vein stripping.

As with safety outcomes, it should be mentioned that differences may exist between treatment of the great and small saphenous veins. While no comparative study included in the present review treated the small saphenous vein, a study by van Rij et al (2003) reported notably higher rates of recurrence after stripping of the small saphenous vein than after stripping the great saphenous vein, at 3- to 6-week and 3-year follow-up.

From the literature available ELT appears to be potentially more effective in the short term, and at least as effective overall, as the comparative procedure of junction ligation and vein stripping for the treatment of varicose veins.

Cost-effectiveness

The cost-effectiveness analysis was derived from the clinical effectiveness data previously described. From this analysis ELT appears to be at least as effective as the comparator, with potentially reduced short-term postoperative pain and faster resumption of normal activities.

A cost-analysis was conducted based on the assumption of no significant differences between treatments in primary clinical outcomes. Based on a number of estimates and assumptions, receiving ELT rather than surgical vein stripping for the treatment of unilateral varicose veins is associated with a modest cost saving (estimated incremental cost per patient = -$171), despite ELT being associated with the higher procedural fee, capital cost of the ELT equipment, duplex ultrasound, additional sclerotherapy and disposable laser fibre and catheters. These costs are offset by reduced staffing costs and a saving in the cost of day surgery, as opposed to hospitalisation.

The potential impact of ELT on the Australian healthcare system was also examined; clinical opinion suggests a short-term increase in demand for varicose vein treatment after the addition of ELT to the MBS, up to a maximum of 50 per cent above current levels in the first year (estimated additional cost to the healthcare system of $18,868,000), decreasing to 10 per cent above current levels in the third year and stabilising after that period.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness for endovenous laser therapy for varicose veins compared with saphenous junction ligation with or without vein stripping.

MSAC finds that endovenous laser therapy is at least as safe, effective and cost-effective as saphenous junction ligation and vein stripping for the treatment of varicose veins.

MSAC recommends that public funding is supported for endovenous laser therapy.

The Minister for Health and Ageing accepted this recommendation on 20 May 2008.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Associate Professor Michael Cleary	emergency medicine
Associate Professor Paul Craft	clinical epidemiology and oncology
Professor Geoff Farrell	gastroenterology
Dr Kwun Fong	thoracic medicine
Professor Richard Fox	medical oncology
Dr David Gillespie	gastroenterology
Dr Bill Glasson	ophthalmologist
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Associate Professor Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Frederick Khafagi	nuclear medicine
Dr Ray Kirk	health research
Dr Ewa Piejko	general practice
Dr Ian Prosser	haematology

Ms Sheila Rimmer	consumer health issues
Dr Judy Soper	radiology
Professor Ken Thomson	radiology
Dr Mary Turner	Australian Health Ministers' Advisory Council representative
Dr David Wood	orthopaedics
Mr Peter Woodley	Assistant Secretary, Medical Benefits Schedule (MBS) Policy Development Branch, Department of Health and Ageing

Appendix B Advisory panel

Advisory panel for MSAC Application 1113: Endovenous laser therapy (ELT) for varicose veins

Dr David Wood (Chair) MBBS, FRACS, FA(Orth)A Orthopaedic Surgeon	Member of MSAC
Dr Ewa Piejko (Second Chair) MBBS, FRACGP General Practitioner	Member of MSAC Nominated by the Royal Australian College of General Practitioners
Mr Peter Milne FRACS, FRCS(Eng), FACS, Fellowship – Cardiovascular Surgery (Baylor College), Member of International Society of Vascular Surgeons and Melbourne Vascular Surgery Association Vascular Surgeon	Co-opted vascular surgeon
Professor Kenneth A Myers MS, FACS, FRACS Vascular Surgeon	Nominated by the Royal Australasian College of Surgeons
Ms Jill Forck Consumer Representative Consumers' Health Forum of Australia	Nominated by the Consumers' Health Forum of Australia

Appendix C Approach to Assessment

Search strategy

Table 24 Bibliographic databases searched

Electronic Database	Time period
AustHealth – including: Australian Medical Index, APAIS Health	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
CINAHL	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
Cochrane Library – including: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
Current Contents Connect	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1998 – 8/2007
EMBASE	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
Medline	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
PubMed	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007
Web of Science – Science Citation Index Expanded	ELT search: 9/2003 – 8/2007 Ligation/stripping search: 1/1997 – 8/2007

APAIS – Australian Public Affairs Information Service; ELT – Endovenous laser therapy; NHS – National Health Service

Table 25 Electronic internet databases searched

Electronic Database	Internet address
Centre for Reviews and Dissemination (CRD) / International Network of Agencies for Health Technology Assessment (INAHTA) databases – including: NHS Economic Evaluation Database (NHS EED) / Database of Abstracts of Reviews of Effect (DARE) / Heath Technology Assessment (HTA) Database	http://www.york.ac.uk/inst/crd/
National Health and Medical Research Council (NHMRC) (Australia)	http://www.health.gov.au/nhmrc/
Australian Department of Health and Ageing	http://www.health.gov.au/
Scirus – for Scientific Information Only	http://www.scirus.com
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services / Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/pages/grey_literature_report
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/

Table 26 Health technology assessment internet sites

Specialist Vascular Websites
• American Venous Forum http://www.venous-info.com/
• Society of Interventional Radiology http://www.sirweb.org/
• Society for Vascular Surgery http://www.vascularweb.org/
Argentina
• Institute for Clinical Effectiveness and Health Policy (IECS) http://www.iecs.org.ar/iecs-visor-publicaciones-ing.php
Australia
• Adelaide Health Technology Assessment (AHTA) http://www.health.adelaide.edu.au/publichealth/consult/health_techn_assess.html
• Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/asernip-s.htm
• Centre for Clinical Effectiveness, Monash University http://www.mihsr.monash.org/cce/
• Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
• Medical Services Advisory Committee (MSAC) http://www.msac.gov.au
Austria
• Institute of Technology Assessment (ITA) http://www.oeaw.ac.at/ita/e1-3.htm
Brazil
• Departamento de Ciência e Tecnologia (DECIT) http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1088
Canada
• Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
• Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications/
• Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home
• Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca
• Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
• Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
• Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
• Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
• Institute of Health Economics (IHE) http://www.ihe.ca/
• Ministry of Health and Long-Term Care – Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
Denmark
• Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.dacehta.dk
• Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
Finland
• Finnish Office for Health Technology Assessment (FinOHTA) http://finohta.stakes.fi/EN/index.htm
France
• Committee for Evaluation and Diffusion of Innovative Techniques (CEDIT) http://cedit.aphp.fr/english/index_present.html
• French National Authority for Health (HAS) http://www.has-sante.fr
Germany
• German Agency for Health Technology Assessment (DAHTA) http://www.dimdi.de/dynamic/en/hta/db/index.htm
Hungary
• Unit of Health Economics and Technology Research Assessment (HunHTA) http://hecon.uni-corvinus.hu/corvinus.php?lng=en

The Netherlands
• Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php?phpLang=en
• Netherlands Organisation for Health Research and Development (ZonMw) http://www.zonmw.nl/en/home.html
New Zealand
• New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
Norway
• Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=84&expand=14,38,84
Spain
• Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud Carlos III / Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
• Andalusian Agency for Health Technology Assessment (AETSA) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp?V=EN
• Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatrm.es/cgi-bin/frame.pl/ang/pu.html
Sweden
• Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp
• Center for Medical Health Technology Assessment http://www.cmt.liu.se/english/publications
Switzerland
• Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/
United Kingdom
• Health Technology Board for Scotland http://www.htbs.co.uk/
• National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.ncchta.org/
• University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
• National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm
United States
• Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
• Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
• U.S. Blue Cross/ Blue Shield Association Technology Evaluation Centre (TEC) http://www.bcbs.com/betterknowledge/tec/
• Veterans' Affairs Technology Assessment Program (VATAP) http://www.va.gov/vatap/publications.htm

Inclusion criteria

Table 27 Inclusion criteria for identification of relevant studies: safety

Characteristic	Criteria
Publication type	*ELT*: Systematic reviews and clinical studies (including randomised and non-randomised comparative studies and case series) will be included. Case series will be included for safety outcomes alone. *Comparator*: Systematic reviews and clinical studies (including randomised and non-randomised comparative studies) will be included. Case series of 100 or more participants will be included for safety outcomes alone. Non-systematic reviews, case reports, articles identified as preliminary reports where results are published in later versions, articles in abstract form, letters, editorials, and animal, in-vitro and laboratory studies will be excluded.
Patient	Patients with documented primary venous reflux of the great or small saphenous veins, in whom sclerotherapy is unlikely to be successful.
Intervention	ELT for the treatment of saphenous reflux, incorporating lasers of all appropriate wavelengths (ie 810, 940, 980, 1064, and 1320 nm).
Comparator	Surgical saphenous stripping and/or junction ligation of varicose veins.
Outcome	Any clinically-related outcomes including but not limited to short- and long-term safety (eg mortality rates, postoperative infection, laser-related adverse effects, thrombotic events, bleeding complications, pain, etc.).
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles.

ELT – Endovenous laser therapy

Table 28 Inclusion criteria for identification of relevant studies: effectiveness

Characteristic	Criteria
Publication type	*ELT*: Systematic reviews and clinical studies (including randomised and non-randomised comparative studies) will be included. *Comparator*: Systematic reviews and clinical studies (including randomised and non-randomised comparative studies) will be included. Non-systematic reviews, case series, case reports, articles identified as preliminary reports where results are published in later versions, articles in abstract form, letters, editorials, and animal, in-vitro and laboratory studies will be excluded.
Patient	Patients with documented primary venous reflux of the great or small saphenous veins, in whom sclerotherapy is unlikely to be successful.
Intervention	ELT for the treatment of saphenous reflux, incorporating lasers of all appropriate wavelengths (ie 810, 940, 980, 1064, and 1320 nm).
Comparator	Surgical saphenous stripping and/or junction ligation of varicose veins.
Outcome	Any clinically-related outcomes including but not limited to short- and long-term effectiveness (eg abolition of reflux, recurrence of varicose veins, recanalisation, reduction of symptoms, quality of life, etc.).
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles.

ELT – Endovenous laser therapy

Appendix D Search strategies

Searching on endovenous laser treatment

#1	Search venous insufficiency Field: MeSH Terms
#2	Search saphenous vein Field: MeSH Terms
#3	Search varicose veins Field: MeSH Terms
#4	Search #1 OR #2 OR #3
#5	Search saphenous near vein* Field: Text Word
#6	Search varicose near vein* Field: Text Word
#7	Search venous near (reflux or incomp* or insuff*) Field: Text Word
#8	Search #5 OR #6 OR #7
#9	Search #4 OR #8
#10	Search laser surgery Field: MeSH Terms
#11	Search vascular surgical procedures Field: MeSH Terms
#12	Search #10 OR #11
#13	Search endovenous* Field: Text Word
#14	Search laser* Field: Text Word
#15	Search EVLT Field: Text Word
#16	Search endovasc* Field: Text Word
#17	Search #13 OR #14 OR #15 OR #16
#18	Search #12 OR #17
#19	Search #9 AND #18 Limits: Human, Published 2003 onwards

Searching on junction ligation and vein stripping

#1	Search venous insufficiency Field: MeSH Terms
#2	Search saphenous vein Field: MeSH Terms
#3	Search varicose veins Field: MeSH Terms
#4	Search #1 OR #2 OR #3
#5	Search saphenous near vein* Field: Text Word
#6	Search varicose near vein* Field: Text Word
#7	Search venous near (reflux or incomp* or insuff*) Field: Text Word
#8	Search #5 OR #6 OR #7
#9	Search #4 OR #8
#10	Search surgical procedures, operative Field: MeSH Terms
#11	Search vascular surgical procedures Field: MeSH Terms
#12	Search ligation Field: MeSH Terms
#13	Search #10 OR #11 OR #12
#14	Search strip* Field: Text Word
#15	Search junction lig* Field: Text Word
#16	Search junction near ligation Field: Text Word
#17	Search #14 OR #15 OR #16
#18	Search #13 OR #17
#19	Search #9 AND #18 Limits: Human, English, Published 1997 onwards

Appendix E Studies excluded from the review

Comparative studies

Technique not examined in review

Passman MA, Dattilo JB et al (2007). Combined endovenous ablation and transilluminated powered phlebectomy: is less invasive better? *Vascular and Endovascular Surgery,* 41(1): 41-47.

Duplicate study

de Medeiros CA & Luccas GC (2005). Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. *Dermatologic Surgery,* 31(12): 1685-1694.

ELT studies

Descriptive studies or review of technique

Eifell RG, Bhattacharya V & Stansby GP (2006). Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for long saphenous vein varices. (Protocol) *Cochrane Database of Systematic Reviews 2006*, Issue 1. Art No. CD005624. DOI: 10.1002/14651858.CD005624.

Min RJ & Khilnani NM (2005). Endovenous laser ablation of varicose veins. *Journal of Cardiovascular Surgery,* 46(4): 395-405.

Inappropriate outcomes reported or no objective assessment of outcomes

Bush RG, Shamma HN & Hammond KA (2005). 940-nm laser for treatment of saphenous insufficiency: histological analysis and long-term follow-up. *Photomedicine and Laser Surgery,* 23(1): 15-19.

Gradman WS (2007). Adjunctive proximal vein ligation with endovenous obliteration of great saphenous vein reflux: does it have clinical value? *Annals of Vascular Surgery,* 21(2): 155-158.

Labropoulos N, Bhatti A et al (2006). Neovascularization after great saphenous vein ablation. *European Journal of Vascular and Endovascular Surgery,* 31(2): 219-222.

Proebstle TM, Krummenauer F et al (2004). Nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. *Dermatologic Surgery,* 30(2 Pt 1): 174-178.

Perforator veins

Almeida JI & Raines JK (2006). Radiofrequency ablation and laser ablation in the treatment of varicose veins. *Annals of Vascular Surgery,* 20(4): 547-552.

Proebstle TM & Herdemann S (2007). Early results and feasibility of incompetent perforator vein ablation by endovenous laser treatment. *Dermatologic Surgery,* 33(2): 162-168.

Conference abstract or proceedings

Beale RJ, Russell DA et al (2004). Out-patient endovenous laser treatment for varicose veins due to saphenofemoral and long saphenous incompetence: is this the future? *Annals of the Royal College of Surgeons of England,* 86(2): 132-133.

M Hirokawa, N Sugano et al (2005). A novel endovenous laser treatment of great saphenous vein reflux with a 1320nm Nd:YAG laser and a pull-back device. *Proceedings of 15th World Congress Union Internationale de Phlebologie*, Rio, Brazil, pp. 241-244.

Could not be obtained

Sadick NS & Wasser S (2007). Combined endovascular laser plus ambulatory phlebectomy for the treatment of superficial venous incompetence: a 4-year perspective. *Journal of Cosmetic Laser Therapy,* 9(1): 9-13.

Junction ligation and vein stripping studies

Descriptive studies or review of technique

Balducci D, Mazzetti S et al (2005). Saphenectomy: From day-surgery to the outpatient's department. *Phlebology,* 20(3): 123-126.

Rigby KA, Palfreyman SJ et al (2002). Surgery for varicose veins: use of tourniquet. *Cochrane Database of Systematic Reviews 2002,* Issue 2. Art. No. CD001486. DOI: 10.1002/14651858.CD001486.

Rigby KA, Palfreyman SJ et al (2004). Surgery versus sclerotherapy for the treatment of varicose veins. *Cochrane Database of Systematic Reviews: Reviews 2004*, Issue 4. Art. No.: CD004980. DOI: 10.1002/14651858.CD004980.

Rudstrom H, Bjorck M & Bergqvist D (2007). Iatrogenic vascular injuries in varicose vein surgery: a systematic review. *World Journal of Surgery,* 31(1): 228-233.

Inappropriate outcomes reported or no objective assessment of outcomes

Allaf N & Welch M (2005). Recurrent varicose veins: Inadequate surgery remains a problem. *Phlebology,* 20(3): 138-140.

Belcaro G, Nicolaides AN et al (2002). Flush ligation of the saphenofemoral junction vs simple, distal ligation. A randomised, 10-year, follow-up. The safe study. *Angeiologie,* 54(1): 19-23.

Belcaro G, Cesarone MR et al (2003). Treatments for varicose veins: Surgery, sclerotherapy, foamsclerotherapy and combined (surgery+sclerotherapy) options. A 10-year, prospective, randomised, controlled, follow-up study. The VEDICO* trial and EST (European Sclerotherapy Trial). *Angeiologie,* 55(1): 29-36.

Belcaro G, Cesarone MR et al (2003). Foam-sclerotherapy, surgery, sclerotherapy, and combined treatment for varicose veins: A 10-year, prospective, randomized, controlled, trial (VEDICO* trial). *Angiology,* 54(3): 307-315.

Blomgren L, Johansson G & Bergqvist D (2005). Randomized clinical trial of routine preoperative duplex imaging before varicose vein surgery. *British Journal of Surgery,* 92(6): 688-694.

Blomgren L, Johansson G et al (2005). Changes in superficial and perforating vein reflux after varicose vein surgery. *Journal of Vascular Surgery,* 42(2): 315-320.

Blomgren L, Johansson G & Bergqvist D (2006). Quality of life after surgery for varicose veins and the impact of preoperative duplex: Results based on a randomized trial. *Annals of Vascular Surgery,* 20(1): 30-34.

Blomgren L, Zethraeus N et al (2006). Cost consequences of preoperative duplex examination before varicose vein surgery: A randomized clinical trial. *Phlebology,* 21(2): 90-95.

Brethauer SA, Murray JD et al (2001). Treatment of varicose veins: proximal saphenofemoral ligation comparing adjunctive varicose phlebectomy with sclerotherapy at a military medical center. *Vascular Surgery,* 35(1): 51-58.

Canonico S, Campitiello F & Santoriello A (2003). Feasibility and problems of day-care varicose vein surgery in elderly patients. *Ambulatory Surgery,* 10(3): 163-166.

Cavezzi A, Carigi V & Collura M (2000). Colour flow duplex scanning as a preoperative guide for mapping and for local anaesthesia in varicose vein surgery. *Phlebology,* 15(1): 24-29.

Creton D (2004). A nondraining saphenous system is a factor of poor prognosis for long-term results in surgery of great saphenous vein recurrences. *Dermatologic Surgery,* 30(5): 744-749.

Critchley G, Handa A et al (1997). Complications of varicose vein surgery. *Annals of the Royal College of Surgeons of England,* 79(2): 105-110.

De Maeseneer MG, Ongena KP et al (1997). Duplex ultrasound assessment of neovascularization after saphenofemoral or saphenopopliteal junction ligation. *Phlebology,* 12(2): 64-68.

Dwerryhouse S, Davies B et al (1999). Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. *Journal of Vascular Surgery,* 29(4): 589-592.

Garner JP, Heppell PS & Leopold PW (2003). The lateral accessory saphenous vein - a common cause of recurrent varicose veins. *Annals of the Royal College of Surgeons of England,* 85(6): 389-392.

Hartmann K, Klode J et al (2006). Recurrent varicose veins: sonography-based re-examination of 210 patients 14 years after ligation and saphenous vein stripping. *Vasa,* 35(1): 21-26.

Hirai M, Iwata H & Sawazaki N (2007). Comparison of recurrence rate and hemodynamic effect among various technical approaches for ligations of great saphenous vein in treatment of varicose veins. *Vasa,* 36(1): 23-27.

Jeanneret C, Fischer R et al (2003). Great saphenous vein stripping with liberal use of subfascial endoscopic perforator vein surgery (SEPS). *Annals of Vascular Surgery,* 17(5): 539-549.

MacKenzie RK, Paisley A et al (2002). The effect of long saphenous vein stripping on quality of life. *Journal of Vascular Surgery,* 35(6): 1197-1203.

Miyazaki K, Nishibe T et al (2003). Stripping operation with sclerotherapy for primary varicose veins due to greater saphenous vein reflux: three-year results. *World Journal of Surgery,* 27(5): 551-553.

Miyazaki K, Nishibe T et al (2004). Hemodynamic changes in stripping operation or saphenofemoral ligation of the greater saphenous vein for primary varicose veins. *Annals of Vascular Surgery,* 18(4): 465-469.

Miyazaki K, Nishibe T et al (2005). Long-term results of treatments for varicose veins due to greater saphenous vein insufficiency. *International Angiology,* 24(3): 282-286.

Sains PS, Reddy KM et al (2005). Audit of varicose vein surgery: the patients' perspective. *Phlebology,* 20(4): 179-182.

Samson RH, Yunis JP & Showalter DP (1998). Is thigh saphenectomy a necessary adjunct to high ligation and stab avulsion phlebectomy? *American Journal of Surgery,* 176(2): 168-171.

Winterborn RJ, Foy C & Earnshaw JJ (2004). Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *Journal of Vascular Surgery,* 40(4): 634-639.

Wright AP, Berridge DC & Scott DJA (2006). Return to Work Following Varicose Vein Surgery: Influence of Type of Operation, Employment and Social Status. *European Journal of Vascular and Endovascular Surgery,* 31(5): 553-557.

Wright D, Gobin JP et al (2006). Varisolve (R) polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. *Phlebology,* 21(4): 180-190.

Wright DDI, Rose KG et al (2001). Recurrence following varicose vein surgery. *Phlebology,* 16(3): 101-105.

Technique not examined in review

Breuninger H (2001). Cryostripping of the long saphenous vein with a percutaneously guided probe. *Dermatologic Surgery,* 27(6): 545-548.

Duplicate study

Michaels JA, Brazier JE et al (2006). Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. *British Journal of Surgery,* 93(2): 175-181.

Appendix F Studies included in the review

Comparative studies

Level II studies

de Medeiros CAF (2006). Comparison of endovenous laser therapy vs. conventional stripping of the great saphenous vein: Midterm results. *Jornal Vascular Brasileiro,* 5(4): 277-287.

Rasmussen LH, Bjoern L et al (2007). Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short-term results. *Journal of Vascular Surgery,* 46(2): 308-315.

Level III studies

Mekako AI, Hatfield J et al (2006). A nonrandomised controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins. *Annals of Vascular Surgery,* 20(4): 451-457.

Vuylsteke M, Van Den BD et al (2006). Endovenous laser obliteration for the treatment of primary varicose veins. *Phlebology,* 21(2): 80-87.

Wu LP, Huang ZH et al (2005). Comparison of immediate therapeutic effects of endovenous laser treatment and conventional therapy for lower extremity varicose veins. *Di Yi Jun Yi Da Xue Xue Bao,* 25(7): 889-891.

ELT studies

Level IV studies

Agus GB, Mancini S & Magi G (2006). The first 1000 cases of Italian endovenous-laser working group (IEWG). Rationale, and long-term outcomes for the 1999-2003 period. *International Angiology,* 25(2): 209-215.

Beale RJ, Mavor AID & Gough MJ (2006). Heat dissipation during endovenous laser treatment of varicose veins - Is there a risk of nerve injury? *Phlebology,* 21(1): 32-35.

Corcos L, Dini S et al (2005). The immediate effects of endovenous diode 808-nm laser in the greater saphenous vein: morphologic study and clinical implications. *Journal of Vascular Surgery,* 41(6): 1018-1024.

Desmyttere J, Grard C & Mordon S (2005). A 2 years follow-up study of endovenous 980-nm laser treatment of the great saphenous vein: Role of the blood content in the GSV. *Medical Laser Application,* 20(4): 283-289.

Disselhoff BC, der Kinderen DJ & Moll FL (2005). Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment? *Journal of Endovascular Therapy,* 12(6): 731-738.

Gibson KD, Ferris BL et al (2007). Endovenous laser treatment of the short saphenous vein: efficacy and complications. *Journal of Vascular Surgery,* 45(4): 795-801.

Goldman MP, Mauricio M & Rao J (2004). Intravascular 1320-nm laser closure of the great saphenous vein: a 6- to 12-month follow-up study. *Dermatologic Surgery,* 30(11): 1380-1385.

Huang Y, Jiang M et al (2005). Endovenous laser treatment combined with a surgical strategy for treatment of venous insufficiency in lower extremity: a report of 208 cases. *Journal of Vascular Surgery,* 42(3): 494-501.

Kabnick LS (2006). Outcome of different endovenous laser wavelengths for great saphenous vein ablation. *Journal of Vascular Surgery,* 43(1): 88-93.

Kavuturu S, Girishkumar H & Ehrlich F (2006). Endovenous laser ablation of saphenous vein is an effective treatment modality for lower extremity varicose veins. *American Journal of Surgery,* 72(8): 672-675.

Kim HS & Paxton BE (2006). Endovenous laser ablation of the great saphenous vein with a 980-nm diode laser in continuous mode: early treatment failures and successful repeat treatments. *Journal of Vascular and Interventional Radiology,* 17(9): 1449-1455.

Kim HS, Nwankwo IJ et al (2006). Lower energy endovenous laser ablation of the great saphenous vein with 980 nm diode laser in continuous mode. *Cardiovascular and Interventional Radiology,* 29(1): 64-69.

Leelaudomlipi S, Sriphojanart S et al (2005). Preminary report: initial experience of endovascular laser therapy for varicose veins due to greater saphenous vein incompetence in Thailand. *Journal of the Medical Association of Thailand,* 88(4): 473-477.

Marston WA, Owens LV et al (2006). Endovenous saphenous ablation corrects the hemodynamic abnormality in patients with CEAP clinical class 3-6 CVI due to superficial reflux. *Vascular and Endovascular Surgery,* 40(2): 125-130.

Mekako A, Hatfield J et al (2006). Combined endovenous laser therapy and ambulatory phlebectomy: refinement of a new technique. *European Journal of Vascular and Endovascular Surgery,* 32(6): 725-729.

Myers K, Fris R & Jolley D (2006). Treatment of varicose veins by endovenous laser therapy: assessment of results by ultrasound surveillance. *Medical Journal of Australia,* 185(4): 199-202.

Oh CK, Jung DS et al (2003). Endovenous laser surgery of the incompetent greater saphenous vein with a 980-nm diode laser. *Dermatologic Surgery,* 29(11): 1135-1140.

Perkowski P, Ravi R et al (2004). Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single-center experience. *Journal of Endovascular Therapy,* 11(2): 132-138.

Petronelli S, Prudenzano R et al (2006). Endovenous laser therapy of the incompetent great saphenous vein. *La Radiologia Medica,* 111(1): 85-92.

Proebstle TM, Gul D et al (2003). Infrequent early recanalization of greater saphenous vein after endovenous laser treatment. *Journal of Vascular Surgery,* 38(3): 511-516.

Proebstle TM, Moehler T et al (2005). Endovenous treatment of the great saphenous vein using a 1,320 nm Nd:YAG laser causes fewer side effects than using a 940 nm diode laser. *Dermatologic Surgery,* 31(12): 1678-1683.

Proebstle TM, Moehler T & Herdemann S (2006). Reduced recanalization rates of the great saphenous vein after endovenous laser treatment with increased energy dosing: definition of a threshold for the endovenous fluence equivalent. *Journal of Vascular Surgery,* 44(4): 834-839.

Puggioni A, Kalra M et al (2005). Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. *Journal of Vascular Surgery* 42(3): 488-493.

Ravi R, Rodriguez-Lopez JA et al (2006). Endovenous ablation of incompetent saphenous veins: a large single-center experience. *Journal of Endovascular Therapy,* 13(2): 244-248.

Sadick NS & Wasser S (2004). Combined endovascular laser with ambulatory phlebectomy for the treatment of superficial venous incompetence: a 2-year perspective. *Journal of Cosmetic Laser Therapy,* 6(1): 44-49.

Salimi J, Yourdkhani F & Moosavi K (2006). Prospective evaluation of endo venous laser therapy for varicose vein; early efficacy and complications. The first report from Iran. *Iranian Journal of Radiation Research,* 4(2): 87-91.

Sharif MA, Soong CV et al (2006). Endovenous laser treatment for long saphenous vein incompetence. *British Journal of Surgery,* 93(7): 831-835.

Siani A, Flaishman I et al (2006). Indications and results of endovenous laser tratment (EVLT) for greater saphenous vein incompetentce. Our experience. *Minerva Cardioangiologica,* 54(3): 369-376.

Soracco JE, D'Ambola JL et al (2005). Complications evidenced in the endovascular laser treatment for varicose veins. *Jornal Vascular Brasileiro,* 4(4): 333-335.

Spartera C, Mastromarino A et al (2006). Endovenous laser treatment (EVLT) in saphenous vein insufficiency. Preliminary study. *European Surgery - Acta Chirurgica Austriaca Supplement,* 38(3): 210-212.

Theivacumar NS, Beale RJ et al (2007). Initial experience in endovenous laser ablation (EVLA) of varicose veins due to small saphenous vein reflux. *European Journal of Vascular & Endovascular Surgery,* 33(5): 614-618.

Timperman PE, Sichlau M & Ryu RK (2004). Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. *Journal of Vascular and Interventional Radiology,* 15(10): 1061-1063.

Timperman PE (2005). Prospective evaluation of higher energy great saphenous vein endovenous laser treatment. *Journal of Vascular and Interventional Radiology,* 16(6): 791-794.

Viarengo LMA, Meirelles GV & Poterio FJ (2006). Treatment of varicose veins with endovenous laser: A prospective 39-month follow-up study. *Jornal Vascular Brasileiro,* 5(3): 184-193.

Yang CH, Chou HS & Lo YF (2006). Incompetent great saphenous veins treated with endovenous 1,320-nm laser: results for 71 legs and morphologic evolvement study. *Dermatologic Surgery,* 32(12): 1453-1457.

Junction ligation and vein stripping studies

Level IV studies

Ahmad I, Ahmad W & Dingui M (2006). Prevention or reversal of deep venous insufficiency by aggressive treatment of superficial venous disease. *American Journal of Surgery,* 191(1): 33-38.

Biswas S, Clark A & Shields DA (2007). Randomised Clinical Trial of the Duration of Compression Therapy after Varicose Vein Surgery. *European Journal of Vascular & Endovascular Surgery,* 33(5): 631-637.

Butler CM, Scurr JH & Coleridge Smith PD (2002). Prospective randomised trial comparing conventional (babcock) stripping with inverting (pin) stripping of the long saphenous vein. *Phlebology,* 17(2): 59-63.

Canonico S, Luminello F et al (2000). Long-term recurrence and nerve injury after total and partial stripping of the great saphenous vein by external phleboextractor. *Vascular Surgery,* 34(2): 163-166.

Chang JB & Stein TA (2002). Management of varicose veins from chronic venous insufficiency. *International Journal of Angiology,* 11(4): 234-237.

Chang JB & Stein TA (2006). Management of varicose veins by high ligation, sclerotherapy and duplex scanning. *Journal for Vascular Ultrasound,* 30(2): 71-74.

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Appendix G Clinical trials and health technology assessments of ELT

Clinical trials

Completed

Beale R, Theivacumar N et al (2006). Endovenous laser treatment (EVLT) or surgery for varicose veins? A randomized controlled trial in patients with saphenofemoral and long saphenous incompetence. *British Journal of Surgery*, 93(3): 380 (conference abstract).

Gough M (contact person), Leeds Vascular Institute, UK. 'Endovenous laser treatment for varicose veins - Follow up questionnaire: The patient perspective.' Reported completion October 2004, see National Research Register for more information, identifier N0436133165.

Homer-Vanniasinkam S (contact person), Leeds Vascular Institute, UK. 'Histological evaluation of Endovenous Laser Treatment (EVLT).' Reported completion April 2004, see National Research Register for more information, identifier N0436133174.

Theivacumar N (contact person), Leeds Vascular Institute, UK. 'Randomised controlled trial of standard EndoVenous Laser Ablation (EVLA) versus standard EVLA with below-knee foam sclerotherapy versus above and below-knee EVLA for varicose veins.' Reported completion May 2007, see Controlled-Trials.com for more information, identifier ISRCTN31316759.

Ongoing

Braithwaite BD (contact person), Department of Vascular Surgery and Endovascular Surgery, Nottingham, UK. 'Randomised control comparison study of endoluminal laser versus foam sclerotherapy in treatment of varicose veins'. Expected completion October 2007, see National Research Register for more information, identifier N0192187950.

Goode S (contact person), University Hospital, UK. 'Laser and radiofrequency vein ablation: A randomised double blind patient controlled trial of radiofrequency closure compared with endovenous laser for the treatment of primary and recurrent great saphenous varicose veins.' Expected completion August 2009, see National Research Register for more information, identifier N0192196071.

Gough M (contact person), Leeds Vascular Institute, UK. 'RCT comparing modified EVLT (endovenous laser treatment) techniques with standard EVLT technique'. Expected completion October 2007, see National Research Register for more information, identifier N0436169958.

Mekako A (contact person), Hull Royal Infirmary, UK. 'A randomised controlled trial of the clinical and cost effectiveness of endovenous laser therapy in the treatment of varicose veins secondary to isolated sapheno-popiteal incompetence and short saphenous

reflux.' Expected completion September 2007, see National Research Register for more information, identifier N0084174061.

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Recruiting

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Health technology assessments

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Appendix H Results of assessment

Critical appraisal of comparative studies

Table 29 Critical appraisal summary of comparative studies – study design details

Study	Randomisation details	Blinding	Sample size	Participants	Interventions and outcomes
de Medeiros (2006)	Lots were drawn by surgeon to determine the surgical technique to be used on each limb (note: all patients underwent surgery using both techniques, one on each limb)	Patient blinded to surgical technique used on each limb Examiners performing post-procedure ultrasound and air plethysmography blinded to study data	N = 20 patients (40 limbs) (ELT: 20 limbs; Comparator: 20 limbs)	Eligibility criteria described Groups well matched at baseline (same patients received both techniques, clinical characteristics of limbs well matched)	Details of interventions provided Primary outcomes defined
Mekako et al (2006b)	Patients allocated to treatment on historical basis (treated with surgery until commencement of ELT treatment at institution)	NR	N = 132 patients (ELT: 70; Comparator: 62)	Eligibility criteria not described Groups moderately matched at baseline (well matched for demographics, clinical characteristics appear comparable, some differences in quality of life scores)	Details of interventions provided Primary outcomes defined
Rasmussen et al (2007)	Randomisation through use of blocks of 10 sealed envelopes	Study not blinded	N = 121 patients (137 limbs) (ELT: 62 patients, 69 limbs; Comparator: 59 patients, 68 limbs)	Eligibility criteria described Groups well matched at baseline (well matched for demographics and clinical characteristics)	Details of interventions provided Primary and secondary outcomes defined
Vuylsteke et al (2006)	Method of allocation not reported	Patient's general practitioner (who controlled duration of sick leave) not informed that duration of sick leave was an outcome of the study	N = 164 patients (242 limbs) (ELT: 80 patients, 118 limbs; Comparator: 84 patients, 124 limbs)	Eligibility criteria described Groups well matched at baseline (well matched for demographic and clinical characteristics within unilaterally and bilaterally affected patient groups)	Details of interventions provided Primary outcomes defined
Wu et al (2005)	Patients allocated to treatment on historical basis (patients treated with L/S Jan 2003 – Sep 2003; patients treated with ELT Oct 2003 – Apr 2004)	NR	N = 50 patients (58 limbs) (ELT: 20 patients, 22 limbs; Comparator: 30 patients, 36 limbs)	Eligibility criteria not described Groups well matched at baseline (well matched for demographics and clinical characteristics)	Details of ELT provided, details of comparator not provided Primary outcomes not defined

ELT – Endovenous laser therapy; NR – Data not reported; L/S – Ligation/stripping

Table 30 Critical appraisal summary of comparative studies – results details

Study	Numbers analysed	Statistical methods	Outcomes and estimations	Ancillary analyses	Adverse events	Follow-up
de Medeiros (2006)	Preliminary sample size calculations performed Intention-to-treat and per-protocol analyses not defined	Tests detailed Significance level defined	Results for each outcome detailed No measures of variability used	No subgroup analyses performed	Described for both groups	Mean: 26 months (range: 4.5-35.5 months) Clinical assessment at 7, 30 and 60 days No losses
Mekako et al (2006b)	Intention-to-treat and per-protocol analyses not defined	Tests detailed Significance level defined	Results for each outcome detailed (clinical outcomes not stratified by treatment) Inter-quartile range as measure of variability	No subgroup analyses performed	Briefly described Losses to follow-up not detailed	Assessment at 1, 6 and 12 weeks Losses to follow-up: ELT: n=21 Comparator: n=33
Rasmussen et al (2007)	Power calculations made before recruitment Comparisons between groups made on an intention-to-treat basis	Tests detailed Significance level defined	Results for each outcome detailed Range and standard deviations as measures of variability	No subgroup analyses performed	Described for both groups Losses to follow-up not detailed	Assessment at 1, 3 and 6 months Losses to follow-up: ELT: n=15 Comparator: n=18
Vuylsteke et al (2006)	Intention-to-treat and per-protocol analyses not defined	Tests detailed Significance level defined	Results for each outcome detailed (outcomes for unilaterally and bilaterally affected patients reported independently; recanalisation and occlusion rates reported for ELT only) Standard deviations as measure of variability	Subgroup analyses performed within unilaterally and bilaterally affected patients comparing effectiveness outcomes of treatments	Described for both groups	Assessment at 1 and 4 weeks and 9 months No losses
Wu et al (2005)	NR	Limited by need for translation Tests detailed Significance level defined	Results for each outcome detailed (complications not reported independently) Range and standard deviations as measures of variability	No subgroup analyses performed	Described for both groups, but reported cumulatively, not independently	Assessment at 12 months No losses

ELT – Endovenous laser therapy; NR – Data not reported

Safety outcomes of comparative studies

Table 31 Major adverse events of comparative studies

Study	Level of evidence	Length of follow-up		Outcome			
				Paraesthesia n (%)	Thrombus extension into femoral vein n (%)	Wound infection n (%)	Groin abscess n (%)
de Medeiros (2006)	II	Mean: 26 months Range: 4.5-35.5	ELT (n=20)	0 (0)	-	-	-
			L/S (n=20)	1 (5)	-	-	-
			P value	-			
Rasmussen et al (2007)	II	6 months	ELT (n=62)	1 (2)	1 (2)	0 (0)	-
			L/S (n=59)	1 (2)	0 (0)	1 (2)	-
			P value	NS	-	-	
Vuylsteke et al (2006)	III-2	9 months	ELT (n=118)	14 (12)	-	-	0 (0)
			L/S (n=128)	28 (23)	-	-	1 (1)
			P value	-			-

ELT: Endovenous laser therapy; L/S: Ligation/stripping; –: Data not reported

Table 32 Minor adverse events of comparative studies

Study	Level of evidence	Length of follow-up		Outcome					
				Bruising / Ecchymosis n (%)	Haematoma n (%)	Oedema n (%)	Phlebitis n (%)	Induration n (%)	Skin burn n (%)
de Medeiros (2006)	II	Mean: 26 months Range: 4.5-35.5	ELT (n=20)	-	4 (20)[a]	3 (15)	-	-	-
			L/S (n=20)	-	12 (60)[a]	8 (40)	-	-	-
			P value		0.03	0.02			
Rasmussen et al (2007)	II	6 months	ELT (n=62)	7 (11)	3 (5)	-	2 (3)	-	-
			L/S (n=59)	15 (25)	5 (8)	-	2 (3)	-	-
			P value	<0.05	NS		NS		
Vuylsteke et al (2006)	III-2	9 months	ELT (n=118)	59 (50)	0 (0)	-	-	23 (19)	3 (3)
			L/S (n=128)	84 (66)	4 (3)	-	-	-	-
			P value	-	-				

ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; –: Data not reported
Values in bold type are significant differences

[a] Values are number of patients reporting large haematoma

Table 33 Pain-related outcomes of comparative studies

Study	Level of evidence	Length of follow-up		Outcome						
				Post-operative pain requiring readmission n (%)	Self-reported pain (12 hours) VAS (1 (min) – 10 (max))	Self-reported pain (7 days) VAS (1 (min) – 10 (max))	Self-reported pain (10 days) VAS (1 (min) – 10 (max))	Mean number of analgesics used (tablets)	Mean time of NSAID usage in days Mean ± SD (range)	Patients requiring analgesics n (%)
de Medeiros (2006)	II	Mean: 26 months Range: 4.5-35.5	ELT (n=20)	-	-	8 / 9 / 3[a]	-	-	-	-
			L/S (n=20)	-	-	8 / 8 / 4[a]	-	-	-	-
			P value			NS				
Mekako et al (2006b)	III-2	12 weeks	ELT (n=70)	0 (0)	-	-	-	-	-	-
			L/S (n=62)	3 (5)	-	-	-	-	-	-
			P value	-						
Rasmussen et al (2007)	II	6 months	ELT (n=62)	-	3.5	2.1	1.7	12.9	-	-
			L/S (n=59)	-	5.0	2.3	1.3	12.0	-	-
			P value		<0.01[b]			NS		
Vuylsteke et al (2006)	III-2	9 months	ELT unilateral (n=118)	-	-	-	-	-	0.7 ± 1.2	-
			L/S unilateral (n=128)	-	-	-	-	-	5.5 ± 5.8	-
			P value						<0.001	
			ELT bilateral (n=118)	-	-	-	-	-	0.9 ± 1.3	-
			L/S bilateral (n=128)	-	-	-	-	-	6.1 ± 6.7	-
			P value						<0.001	
Wu et al (2005)	III-2		ELT (n=20)	-	-	-	-	-	-	6 (30)
			L/S (n=30)	-	-	-	-	-	-	23 (77)
			P value							<0.01

ELT: Endovenous laser therapy; NS: Non-significant; NSAID: Non-steroidal anti-inflammatory drug; L/S: Ligation/stripping; VAS: Visual analogue scale; –: Data not reported

Plus-minus values are mean ± standard deviation; values in bold type are significant differences

[a] Values are number of patients reporting absent / mild / moderate levels of pain

[b] ELT patients reported significantly less pain over entire 10-day follow-up period

Safety outcomes by ELT wavelength

Table 34 Summary of adverse events after ELT by laser wavelength

	Laser wavelength											
	810 nm			940 nm			980 nm			1320 nm		
Adverse event	Studies n	Limbs (patients) n	Affected limbs n (%)	Studies n	Limbs (patients) n	Affected limbs n (%)	Studies n	Limbs (patients) n	Affected limbs n (%)	Studies n	Limbs (patients) n	Affected limbs n (%)
Total	24	2255 (1722)		7	2020 (707)		11	679 (552)		3	128 (103)	
Thromboembolic events												
Pulmonary embolism	5	881 (731)	1 (0.1)	1	263 (203)	0 (0.0)	4	227 (166)	0 (0.0)	1	71 (50)	0 (0.0)
Deep venous thrombosis	10	1272 (1013)	6 (0.5)	5	1662 (430)	0 (0.0)	7	523 (426)	13 (2.5)	1	71 (50)	1 (1.4)
Superficial thrombophlebitis[a]	4	271 (235)	7 (2.6)	1	109 (85)	10 (9.2)	3	109 (86)	4 (3.7)	0	-	-
Nerve events												
Nerve injuries[b]	7	1260 (927)	14 (1.1)	2	269 (227)	1 (0.4)	3	111 (85)	0 (0.0)	0	-	-
Paraesthesia	8	679 (635)	29 (4.3)	2	512 (395)	45 (8.8)	6	617 (529)	26 (4.2)	2	104 (81)	7 (6.7)
Infection events												
Infection/cellulitis	1	31 (30)	0 (0.0)	1	263 (203)	0 (0.0)	2	187 (142)	0 (0.0)	1	71 (50)	0 (0.0)
Bleeding events												
Haematoma	4	152 (119)	5 (3.3)	0	-	-	3	163 (136)	6 (3.7)	0	-	-
Ecchymosis/bruising	5	343 (325)	157 (45.8)	2	512 (395)	397 (77.5)	7	439 (365)	207 (47.2)	1	33 (31)	20 (60.6)
Laser events												
Skin burns	11	1679 (1230)	12 (0.7)	3	368 (265)	1 (0.3)	5	353 (292)	3 (0.8)	1	71 (50)	0 (0.0)
Pain events												
Post-procedural pain[c]	6	389 (357)	47 (13.2)	3	621 (480)	372 (77.5)	2	141 (138)	21 (15.2)	2	57 (53)	16 (30.2)
Other events												
Phlebitis	2	98 (65)	13 (13.3)	2	512 (395)	60 (11.7)	3	225(188)	5 (2.2)	1	33 (31)	3 (9.1)
Induration	1	93 (85)	2 (2.2)	3	621 (480)	362 (58.3)	2	133 (92)	32 (24.1)	1	33 (31)	15 (45.5)
Sensation of tightness	2	124 (115)	26 (21.0)	0	-	-	2	94 (74)	28 (29.8)	0	-	-
Hyperaemia	1	150 (150)	39 (26.0)	0	-	-	0	-	-	0	-	-
Oedema	2	97 (73)	5 (5.2)	0	-	-	0	-	-	0	-	-
Hyperpigmentation/dyschromia	3	557 (347)	25 (4.5)	1	263 (203)	6 (2.3)	1	126 (126)	0 (0.0)	0	-	-

–: Data not reported

[a] Superficial thrombophlebitis also includes superficial venous thrombosis

[b] Nerve injuries contain foot drop, neuritis, neuralgia, sural nerve palsy

[c] Occurrence rate calculations based on number of patients

Effectiveness outcomes of comparative studies

Table 35 Quality of life (SF-36) outcomes – comparative studies

Study	Level of evidence	Length of follow-up	Time point		Outcome							
					SF-36 scores (0 (lowest quality of life) – 100 (highest quality of life))							
					Physical functioning	Role-physical	Bodily pain	General health	Vitality	Social functioning	Role-emotional	Mental health
Mekako et al (2006b)[a]	III-2	12 weeks	Pre-treatment	ELT (n=70)	90 (80-100)	100 (25-100)	74 (51-84)	82 (62-92)	73 (60-80)	100 (75-100)	100 (100-100)	88 (76-92)
				L/S (n=62)	80 (55-91)	75 (50-100)	52 (51-74)	77 (70-87)	60 (40-80)	88 (62-100)	100 (66-100)	84 (67-92)
				P value	0.003	NS	0.009	NS	0.009	NS	NS	NS
			1 week	ELT (n=70)	90 (90-100)	75 (0-100)	72 (42-84)	82 (72-92)	70 (55-80)	88 (75-100)	100 (100-100)	88 (76-92)
				L/S (n=62)	40 (18-75)	0 (0-25)	41 (31-62)	80 (66-87)	55 (38-70)	63 (37-75)	100 (66-100)	84 (68-92)
				P value	< 0.01	< 0.01	< 0.01	NS	NS	< 0.01	NS	NS
			6 weeks	ELT (n=70)	100(90-100)	100 (75-100)	84 (73-100)	86 (74-97)	75 (60-90)	100 (75-100)	100 (100-100)	88 (80-92)
				L/S (n=62)	85 (60-95)	100 (0-100)	74 (62-100)	82 (67-93)	65 (50-80)	100 (68-100)	100 (66-100)	88 (72-92)
				p value	< 0.01	< 0.01	NS	NS	NS	NS	NS	NS
			12 weeks	ELT (n=70)	100 (86-100)	100 (81-100)	92 (72-100)	82 (73-97)	75 (60-85)	100 (75-100)	100 (100-100)	90 (70-96)
				L/S (n=62)	95 (87-100)	100 (100-100)	74 (52-100)	82 (64-91)	70 (55-85)	100 (87-100)	100 (100-100)	88 (80-100)
				P value	NS	NS	NS	NS	NS	NS	NS	NS
Rasmussen et al (2007)[b]	II	6 months	Pre-treatment	ELT (n=62)	87.0 (25-100)	87.0 (25-100)	76.6 (22-100)	65.2 (32-80)	69.0 (12.5-100)	90.4 (25-100)	88.1 (50-100)	79.3 (35-100)
				L/S (n=59)	89.3 (25-100)	89.3 (25-100)	77.1 (22-100)	67.6 (28-80)	73.1 (12.5-100)	95.3 (62.5-100)	91.8 (50-100)	83.3 (35-100)
				P value	-	-	-	-	-	-	-	-
			12 days	ELT (n=62)	70.0 (6.2-100)	69.8 (6.2-100)	59.4 (22-100)	67.4 (41.6-80)	68.1 (12.5-100)	90.4 (0-100)	84.4 (16.7-100)	83.5 (45-100)
				L/S (n=59)	72.1 (0-100)	72.1 (0-100)	52.2 (0-100)	68.0 (24-80)	72.4 (37.5-100)	92.9 (62.5-100)	91.4 (41.7-100)	87.0 (60-100)
				P value	NS	NS	0.042	NS	NS	NS	NS	NS
			1 month	ELT (n=62)	84.8 (25-100)	84.6 (25-100)	78.6 (22-100)	67.2 (29.6-80)	71.3 (0-100)	91.8 (50-100)	90.2 (41.7-100)	84.3 (25-100)
				L/S (n=59)	87.4 (18.8-100)	87.4 (18.7-100)	81.9 (41-100)	67.9 (20-80)	79.1 (25-100)	96.7 (50-100)	92.6 (50-100)	90.4 (65-100)
				P value	NS	NS	NS	NS	NS	NS	NS	NS
			3 months	ELT (n=62)	93.9 (56.2-100)	93.9 (56.2-100)	89.1 (32-100)	67.7 (32-80)	76.2 (18.7-100)	94.5 (37.5-100)	94.4 (33.3-100)	84.3 (25-100)
				L/S (n=59)	92.2 (43.7-100)	92.2 (43.7-100)	89.5 (31-100)	66.7 (20-80)	79.0 (37.5-100)	97.1 (12.5-100)	95.8 (58.3-100)	89.2 (60-100)
				P value	NS	NS	NS	NS	NS	NS	NS	NS
			6 months	ELT (n=62)	93.9 (43.7-100)	93.9 (43.7-100)	90.9 (51-100)	67.9 (40-80)	77.0 (18.7-100)	98.2 (62.5-100)	95.0 (58.3-100)	86.2 (40-100)
				L/S (n=59)	92.6 (50-100)	92.6 (50-100)	86.5 (20-100)	67.0 (33.6-80)	82.9 (56.2-100)	98.8 (62.5-100)	95.7 (50-100)	90.2 (70-100)
				P value	NS	NS	NS	NS	NS	NS	NS	NS

ELT: Endovenous laser therapy; NS: Non-significant; L/S: Ligation/stripping; –: Data not reported
Values in bold type are significant differences

[a] Values for Mekako et al (2006b) are median (inter-quartile range)

[b] Values for Rasmussen et al (2007) are mean (range)

Appendix I Studies reporting adverse events

Thromboembolic events

Pulmonary embolism

Comparative studies

Vuylsteke M, Van Den BD et al (2006). Endovenous laser obliteration for the treatment of primary varicose veins. *Phlebology,* 21(2): 80-87.

ELT studies

Disselhoff BC, der Kinderen DJ & Moll FL (2005). Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment? *Journal of Endovascular Therapy,* 12(6): 731-738.

Huang Y, Jiang M et al (2005). Endovenous laser treatment combined with a surgical strategy for treatment of venous insufficiency in lower extremity: a report of 208 cases. *Journal of Vascular Surgery,* 42(3): 494-501.

Kim HS & Paxton BE (2006). Endovenous laser ablation of the great saphenous vein with a 980-nm diode laser in continuous mode: early treatment failures and successful repeat treatments. *Journal of Vascular and Interventional Radiology,* 17(9): 1449-1455.

Kim HS, Nwankwo IJ et al (2006). Lower energy endovenous laser ablation of the great saphenous vein with 980 nm diode laser in continuous mode. *Cardiovascular and Interventional Radiology,* 29(1): 64-69.

Myers K, Fris R & Jolley D (2006). Treatment of varicose veins by endovenous laser therapy: assessment of results by ultrasound surveillance. *Medical Journal of Australia,* 185(4): 199-202.

Oh CK, Jung DS et al (2003). Endovenous laser surgery of the incompetent greater saphenous vein with a 980-nm diode laser. *Dermatologic Surgery,* 29(11): 1135-1140.

Proebstle TM, Moehler T & Herdemann S (2006). Reduced recanalization rates of the great saphenous vein after endovenous laser treatment with increased energy dosing: definition of a threshold for the endovenous fluence equivalent. *Journal of Vascular Surgery,* 44(4): 834-839.

Puggioni A, Kalra M et al (2005). Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. *Journal of Vascular Surgery* 42(3): 488-493.

Siani A, Flaishman I et al (2006). Indications and results of endovenous laser tratment (EVLT) for greater saphenous vein incompetentce. Our experience. *Minerva Cardioangiologica,* 54(3): 369-376.

Viarengo LMA, Meirelles GV & Poterio FJ (2006). Treatment of varicose veins with endovenous laser: A prospective 39-month follow-up study. *Jornal Vascular Brasileiro,* 5(3): 184-193.

Yang CH, Chou HS & Lo YF (2006). Incompetent great saphenous veins treated with endovenous 1,320-nm laser: results for 71 legs and morphologic evolvement study. *Dermatologic Surgery,* 32(12): 1453-1457.

Junction ligation and vein stripping studies

van Rij AM, Chai J et al (2004). Incidence of deep vein thrombosis after varicose vein surgery. *British Journal of Surgery* 91(12): 1582-1585.

Zbronski R, Matuszewska-Zbronska H et al (2005). Stripping of the long saphenous vein under local anaesthesia - own experience. *Chirurgia Polska,* 7(4): 238-243.

Deep venous thrombosis

Comparative studies

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Superficial thrombophlebitis

ELT studies

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Junction ligation and vein stripping studies

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Nerve events

Nerve injuries

ELT studies

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Paraesthesia

Comparative studies

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Infection events

Infection/Cellulitis

Comparative studies

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Stitch sinus

Junction ligation and vein stripping studies

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Bleeding events

Bleeding complications

Junction ligation and vein stripping studies

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Haematoma

Comparative studies

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Ecchymosis / bruising

Comparative studies

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Junction ligation and vein stripping studies

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Kam MH & Tan SG (2003). Results of long saphenous vein stripping. *Singapore Medical Journal,* 44(12): 639-642.

Laser events

Skin burns

Comparative studies

Vuylsteke M, Van Den BD et al (2006). Endovenous laser obliteration for the treatment of primary varicose veins. *Phlebology,* 21(2): 80-87.

ELT studies

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Pain events

Post-procedural pain

Comparative studies

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Junction ligation and vein stripping studies

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Other events

Phlebitis

Comparative studies

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Induration

Comparative studies

Vuylsteke M, Van Den BD et al (2006). Endovenous laser obliteration for the treatment of primary varicose veins. *Phlebology,* 21(2): 80-87.

ELT studies

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Sensation of tightness

ELT studies

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Hyperemia

ELT studies

Spartera C, Mastromarino A et al (2006). Endovenous laser treatment (EVLT) in saphenous vein insufficiency. Preliminary study. *European Surgery - Acta Chirurgica Austriaca Supplement,* 38(3): 210-212.

Oedema

Comparative studies

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ELT studies

Puggioni A, Kalra M et al (2005). Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. *Journal of Vascular Surgery*, 42(3): 488-493.

Hyperpigmentation / dyschromia

ELT studies

Agus GB, Mancini S & Magi G (2006). The first 1000 cases of Italian endovenous-laser working group (IEWG). Rationale, and long-term outcomes for the 1999-2003 period. *International Angiology,* 25(2): 209-215.

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Junction ligation and vein stripping studies

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Lymphorrhea/seroma

Junction ligation and vein stripping studies

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