National Clinical Guideline Centre

Varicose Veins Appendices

Varicose Veins

Appendices A-O

Appendices

Methods, evidence and recommendations

12th February 2013

Draft for consultation

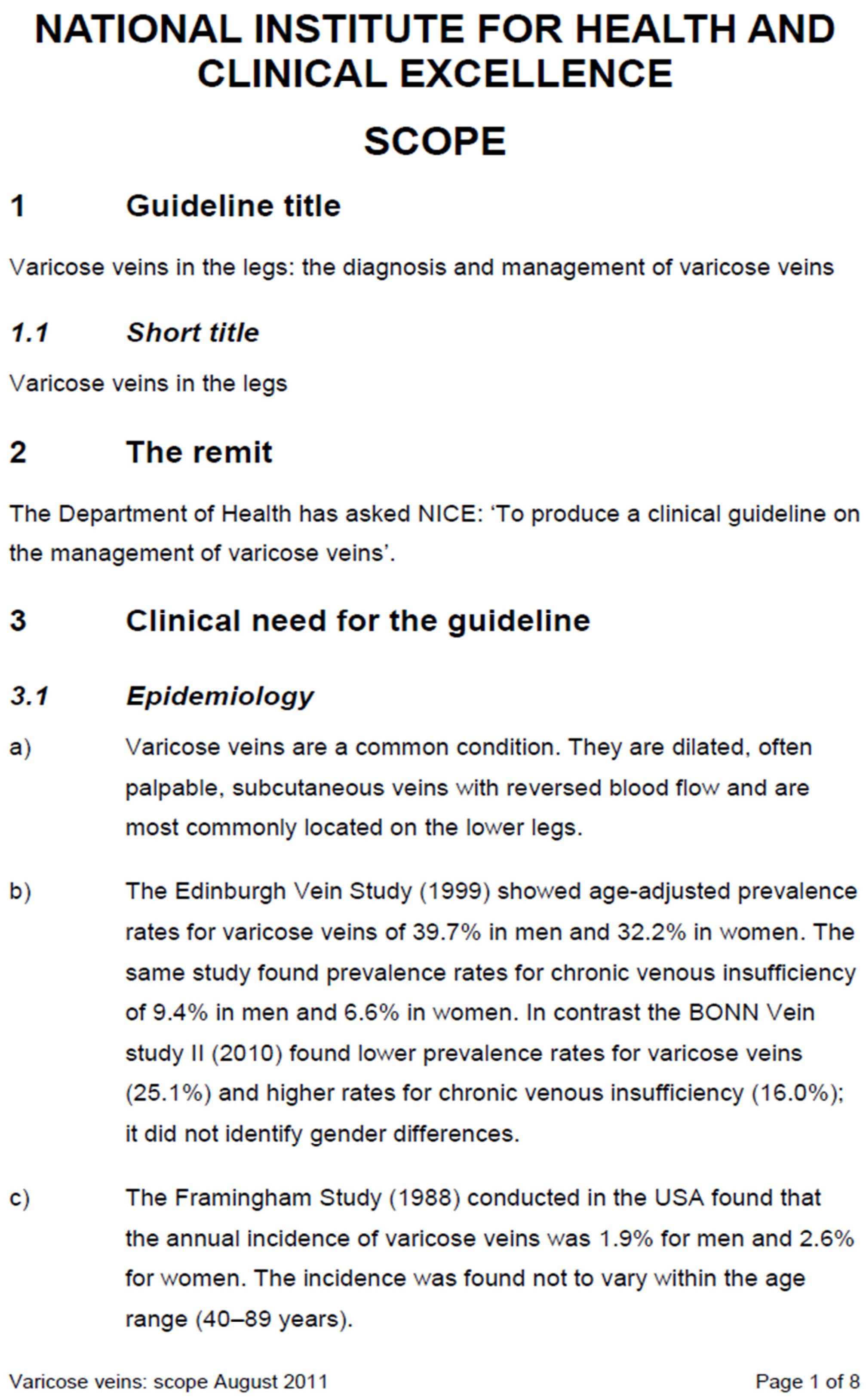
Commissioned by the National Institute for
Health and Clinical Excellence

Funding
National Institute for Health and Clinical Excellence

Contents

Appendices

Appendix A: Scope



NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Varicose veins in the legs: the diagnosis and management of varicose veins

1.1 Short title

Varicose veins in the legs

2 The remit

The Department of Health has asked NICE: ‘To produce a clinical guideline on the management of varicose veins’.

3 Clinical need for the guideline

3.1 Epidemiology

a) Varicose veins are a common condition. They are dilated, often palpable, subcutaneous veins with reversed blood flow and are most commonly located on the lower legs.

b) The Edinburgh Vein Study (1999) showed age-adjusted prevalence rates for varicose veins of 39.7% in men and 32.2% in women. The same study found prevalence rates for chronic venous insufficiency of 9.4% in men and 6.6% in women. In contrast the BONN Vein study II (2010) found lower prevalence rates for varicose veins (25.1%) and higher rates for chronic venous insufficiency (16.0%); it did not identify gender differences.

c) The Framingham Study (1988) conducted in the USA found that the annual incidence of varicose veins was 1.9% for men and 2.6% for women. The incidence was found not to vary within the age range (40–89 years).

Varicose veins: scope August 2011 Page 1 of 8

d) The age of onset does vary and prevalence rises with age. Varicose veins are common during pregnancy and affect about 40% of pregnant women.

e) The clinical presentation of varicose veins differs and some people are asymptomatic. In the majority of people varicose veins do not cause damage or threat to the limb but are associated with aching, itching, burning, cramps at night, and restless legs. In some people with varicose veins, progression of the condition may result in more severe problems such as skin pigmentation changes, eczema, infection, superficial thrombophlebitis, bleeding, loss of subcutaneous tissue, lipodermatosclerosis and venous ulceration.

3.2 Current practice

a) Current management of varicose veins is controversial and there is considerable variation in clinical practice.

b) There is a lack of consensus about optimum indications for referral and treatment. Suitability for varicose vein treatment is mainly determined by clinical examination and followed by a hand held doppler and/or duplex scan to determine whether venous reflux is present. However, there can be an inconsistent association between the symptoms of varicose veins and their severity or size on examination.

c) There are many clinical grading systems for varicose veins, including CEAP (clinical signs, aetiologic classification, anatomic distribution and pathophysiological dysfunction). However, with most of these there is a lack of agreement as to their usefulness for clinical decision making. Although CEAP is the most widely accepted grading system for varicose veins as a way to determine treatment needs, it is not discriminatory when looking at mild forms of the disease or predicting who would benefit the most from intervention.

d) Treatment options include:

- Conservative treatment – this includes diet, lifestyle advice and compression therapy. These are often used as first-line treatments in primary care.
- Pharmacological treatments for the relief of symptoms. There are none currently licensed for use in the UK.
- Interventional procedures:
  - Surgical treatments – these include ligation (tying off the vein), stripping and avulsion (different ways of removing the vein). These operations can be performed under general, regional or local anaesthesia, depending on the preferences of the surgeon and patient, and on the extent and the complexity of the varicose veins to be treated.
  - Sclerotherapy – injecting a sclerosing (irritating) agent directly into the varicose veins. This can be either as liquid or foam. This causes an inflammatory response that closes off the vein.
  - Thermal ablation – heating the vein from inside (for example using radiofrequency or laser catheters), this causes irreversible damage to the vein and its lining and closes it off.

e) Often several of the above techniques are used in combination. Treatment choice depends on a number of factors; symptoms, severity, patient preference and available medical resources.

f) The lack of clarity over assessment and the perceived similarity in outcomes from the different the interventional therapies have led to considerable variation in the management of varicose veins.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 and older) with primary or recurrent varicose veins in their legs.

b) The particular needs of pregnant women will be considered.

4.1.2 Groups that will not be covered

a) Children and young people (younger than 18).

b) People with venous malformations.

c) People with varicose veins in places other than their legs.

4.2 Healthcare setting

a) NHS healthcare settings in which varicose veins are managed.

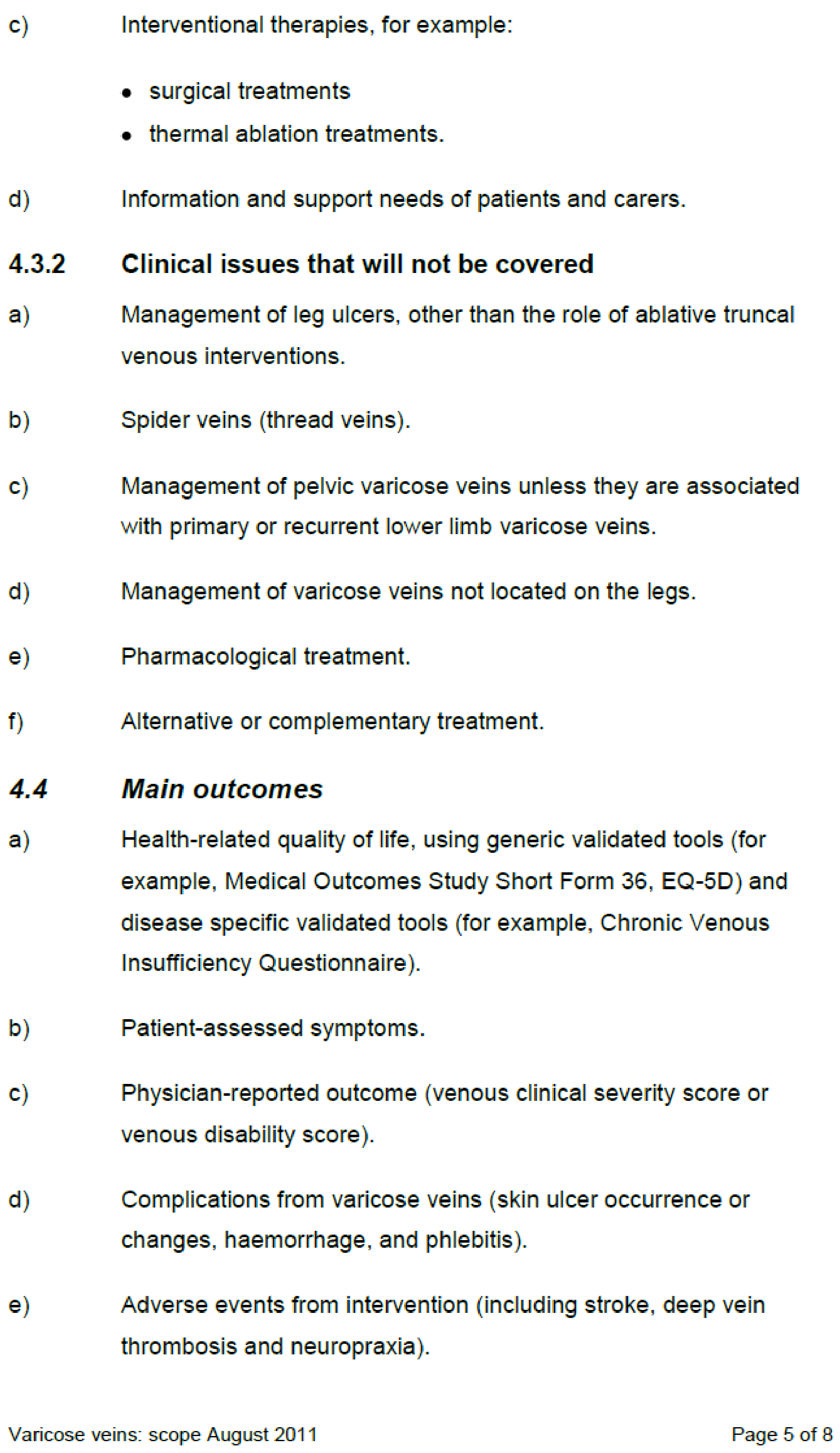
4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Assessment for referral and treatment, including hand held doppler, duplex scan and clinical grading systems.

b) Conservative treatments, including

- lifestyle advice
- compression therapies.



c) Interventional therapies, for example:

- surgical treatments
- thermal ablation treatments.

d) Information and support needs of patients and carers.

4.3.2 Clinical issues that will not be covered

a) Management of leg ulcers, other than the role of ablative truncal venous interventions.

b) Spider veins (thread veins).

c) Management of pelvic varicose veins unless they are associated with primary or recurrent lower limb varicose veins.

d) Management of varicose veins not located on the legs.

e) Pharmacological treatment.

f) Alternative or complementary treatment.

4.4 Main outcomes

a) Health-related quality of life, using generic validated tools (for example, Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (for example, Chronic Venous Insufficiency Questionnaire).

b) Patient-assessed symptoms.

c) Physician-reported outcome (venous clinical severity score or venous disability score).

d) Complications from varicose veins (skin ulcer occurrence or changes, haemorrhage, and phlebitis).

e) Adverse events from intervention (including stroke, deep vein thrombosis and neuropraxia).

f) Recurrent varicose veins.

g) Vein reflux and occlusion (blockage) rates.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in September 2011.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be incorporated

NICE interventional procedure guidance 314 (2009) 'Ultrasound-guided foam sclerotherapy for varicose veins' is being updated and we expect that guidance will be available in late 2012. If the updated guidance recommends that the procedure can be used without the need for special arrangements for clinical governance, consent or research, the interventional procedure guidance will be incorporated into the guideline.

This guideline will also incorporate the following NICE guidance.

- Endovenous laser treatment of the long saphenous vein. NICE interventional procedure guidance 52 (2004). Available from www.nice.org.uk/guidance/IPG52
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedure guidance 37 (2004). Available from www.nice.org.uk/guidance/IPG37
- Radiofrequency ablation of varicose veins. NICE interventional procedure guidance 8 (2003). Available from www.nice.org.uk/guidance/IPG8

5.1.2 Other related NICE guidance

- Promoting physical activity in the workplace. NICE public health guidance 13 (2008). Available from www.nice.org.uk/guidance/PH13
- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10
- Physical activity and the environment. NICE public health guidance 8 (2008). Available from www.nice.org.uk/guidance/PH8
- Obesity. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43
- Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006). Available from www.nice.org.uk/guidance/PH2
- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1
- NICE referral advice recommendations database [online]. Available from www.nice.org.uk/usingguidance/referraladvice/index.jsp

6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of interest

B.1 Professor Alun Davies

GDG meeting	Declaration of Interests	Action taken
On Application	AD declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None Declared	None
Second GDG Meeting [02/11/11]	**Personal pecuniary (non-specific):** Attended and lectured at Turkish Vascular society, European Society of Vascular surgery, European Venous Forum, ARAB vein meeting (Saudi Arabia). The meeting organisers paid expenses but no monies were given for lecturing. The organisers would have had multiple healthcare related sponsors.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary
Third GDG Meeting [14/12/11]	**Personal pecuniary (non-specific):** Expenses paid for attending and lecturing at Veith symposium (USA). The meeting organisers paid expenses but no monies were given for lecturing. The organisers would have had multiple industrial sponsors.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary
Fourth GDG Meeting [25/01/12]	**Personal Pecuniary (non-specific):** Attended academic meeting of CACVS (Controversies and Updates in Vascular Surgery) in France and received expenses for registration, travel and accommodation from meeting organisers, who would have had industrial sponsorship. **Non-personal pecuniary (non-specific):** Research department was awarded a grant from Venous Forum UK.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary. The grant was awarded by an academic body, not involved in the manufacture of varicose veins related equipment. NOF, KK and KH agreed no action was necessary.
Fifth GDG Meeting [07/03/12]	**Personal Pecuniary (non-specific):** Attended American Venous Forum (USA) with registration paid for by meeting organisers who would have had industrial sponsorship. **Non-personal pecuniary (non-specific)**: Met with Sapheon to investigate commencing a trial in the UK on vein ablation with a novel glue technology. A grant has been awarded from Sapheon to Imperial College for which AD is the principle investigator.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary Glue is not a technology under consideration in this guideline and Sapheon do not make any other products used in the management of varicose veins. NOF, KK and KH agreed no action was necessary.

GDG meeting	Declaration of Interests	Action taken
	Non personal pecuniary (non-specific): A grant was awarded to the research department from Clarivein (novel vibrating technology for varicose vein treatment), for which AD is the principle investigator.	The technique under investigation is not a technology under consideration in this guideline and Clarivein do not make any other products used in the management of varicose veins. NOF, KK and KH agreed no action was necessary.
Sixth GDG Meeting [18/04/12]	**Non personal pecuniary (non-specific):-** A grant of was awarded to the research department from Geko to fund a trial looking at an electrical stimulation tool for the prevention of VTE.	The prevention of VTE is not relevant to this guideline and the Geko do not make any other products used in the management of varicose veins. NOF, KK and KH agreed no action was necessary.
	Personal pecuniary (non-specific): Organised and attended major meeting (Charing Cross Symposium) with multiple industrial sponsors and attended meal.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary.
	Personal pecuniary (non-specific): Received a bursary to cover travel and accommodation expenses from Australasian College of Phlebology (ACP) to attend and lecture at their annual meeting (Australia). The meeting organisers who would have had industrial sponsorship.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary
	Personal pecuniary (non-specific): Attended and meeting with Servier (Paris) to discuss Daflon a pharmaceutical treatment of varicose veins. Servier paid travel expenses.	Pharmacological treatments are under consideration in this guideline and Servier do not make any other products used in the management of varicose veins. NOF, KK and KH agreed no action was necessary.
	Personal non-pecuniary (non-specific): Received expenses for travel, registration and accommodation to the European Vascular Course (Belgium) from the meeting organisers. The meeting organisers who would have had industrial sponsorship.	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. NOF, KK and KH agreed no action was necessary
Seventh GDG Meeting [11/07/12]	Did not attend this meeting	No action necessary
Eighth GDG Meeting [03/10/12]	**Personal pecuniary (non-specific):** Attended vascular meeting in India funded by the Indian vascular society and VASCUTEK.	VASCUTEK do not make any venous products. Funding not beyond that reasonably expected. KK and KH agreed no action was necessary
Ninth GDG	No change to declarations of interest.	None

GDG meeting	Declaration of Interests	Action taken
Meeting [07/11/12]		
Tenth GDG Meeting [19/12/12]	**Personal pecuniary (non-specific):** Attended the Veith Vascular Symposium as a guest speaker and gave 7 talks. Fights were funded by VASCUTEK UK and the meeting was sponsored by multiple companies	VASCUTEK do not make any venous products. Funding not beyond that reasonably expected. KK and KH agreed no action was necessary
Eleventh GDG Meeting [10/04/13]		

1 ## B.2 Dr. Mustapha Azzam

GDG meeting	Declaration of Interests	Action taken
On Application	MA declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	None	None
Fifth GDG Meeting [07/03/12]	**Personal pecuniary (non-specific):** Attended a meeting with GEKO to discuss their electrical stimulation device for the prevention of DVT.	The prevention of VTE is not relevant to this guideline and the GEKO do not make any other products used in the management of varicose veins. AD, NOF, KK and KH agreed no action was necessary.
Sixth GDG Meeting [18/04/12]	**Personal pecuniary (non-specific):-** Attended a dinner with representatives of Sapheon.	Sapheon do not make anything under consideration in the guideline. AD, KK and KH agreed no action was necessary.
	Personal pecuniary (non-specific): Attended an advisory board meeting with First Sky Medical	First Sky Medical do not make anything under consideration in the guideline. AD, KK and KH agreed no action was necessary
Seventh GDG Meeting	**Personal pecuniary (non-specific):** Assisted GEKO in setting up a Doppler protocol for a	The prevention of VTE is not relevant to this guideline and GEKO do not make

GDG meeting	Declaration of Interests	Action taken
[11/07/12]	trial of their electrical stimulation device for the prevention of DVT in orthopaedic patients.	any other products used in the management of varicose veins. AD, KK and KH agreed no action was necessary.
Eighth GDG Meeting [03/10/12]	No change to declarations of interest.	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	No change to declarations of interest.	None
Eleventh GDG Meeting [10/04/13]		

1

2 B.3 Professor Andrew Bradbury

GDG meeting	Declaration of Interests	Action taken
On Application	AB declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	Did not attend this meeting	None
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	**Personal pecuniary (Specific):** Attended as part of the faculty the European Venous Forum (EVF) Hands-On Workshop (HOW) in Vienna in November 2011. Travel and accommodation costs were covered by the EVF and those funds were obtained from a range of different companies who manufacture materials and equipment used for the treatment of venous disease.	No direct sponsorship by any manufacturer company involved in varicose veins related products. All sponsorship not considered to be beyond what would reasonably be required for accommodation, meals and travel to attend. AD, NOF and KK agreed no action was necessary.
Fourth GDG Meeting [25/01/12]	No change to declarations of interest.	None
Fifth GDG Meeting [07/03/12]	No change to declarations of interest.	None

GDG meeting	Declaration of Interests	Action taken
Sixth GDG Meeting [18/04/12]	**Non-personal pecuniary (Specific):** Department did some research which was funded by British Biotechnology Group (BTG) Ltd, who are trying to make a commercial foam, looking at the evaluation of a novel health-related quality-of-life (HRQL) instrument administered via a Palmtop Application Device (PAD). The funds were used to pay the salary of a research nurse. No personal payment received	No personal knowledge of the intervention or matter either through his or her own work, or through direct supervision of other people's work. AD, KK and KH agreed no action was required.
Seventh GDG Meeting [11/07/12]	**Personal Non-pecuniary** –Had a discussion with the Chief Executive of STD pharmaceuticals (who make a chemical called STS which can be used to make foam for the treatment of varicose veins) during dinner at the European Venous Forum annual meeting in Florence in June 2012. During that dinner the application of a European licence for STS foam was discussed.	Discussed within the GDG. It was concluded that as the GDG were aware of this declaration and could take it into consideration during the GDG meetings they did not feel that AB should be excluded. AB will remain in the discussion and development of recommendations.
Eighth GDG Meeting [03/10/12]	Did not attend this meeting	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	Did not attend this meeting	None
Eleventh GDG Meeting [10/04/13]		

1

B.4 Dr. Jocelyn Brookes

GDG meeting	Declaration of Interests	Action taken
On Application	JB declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None

GDG meeting	Declaration of Interests	Action taken
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	Did not attend this meeting	None
Fifth GDG Meeting [07/03/12]	None	None
Sixth GDG Meeting [18/04/12]	Did not attend this meeting	None
Seventh GDG Meeting [11/07/12]	None	None
Eighth GDG Meeting [03/10/12]	None	None
Ninth GDG Meeting [07/11/12]	Did not attend this meeting	None
Tenth GDG Meeting [19/12/12]	None	None
Eleventh GDG Meeting [10/04/13]		

B.5 Mrs. Joyce Calam

GDG meeting	Declaration of Interests	Action taken
On Application	JC declared she knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None
Second GDG Meeting	None	None

GDG meeting	Declaration of Interests	Action taken
[02/11/11]		
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	None	None
Fifth GDG Meeting [07/03/12]	None	None
Sixth GDG Meeting [18/04/12]	None	None
Seventh GDG Meeting [11/07/12]	None	None
Eighth GDG Meeting [03/10/12]	None	None
Ninth GDG Meeting [07/11/12]	None	None
Tenth GDG Meeting [19/12/12]	None	None
Eleventh GDG Meeting [10/04/13]		

B.6 Mr. David Evans

GDG meeting	Declaration of Interests	Action taken
On Application	DE declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None

GDG meeting	Declaration of Interests	Action taken
Third GDG Meeting [14/12/11]	**Personal pecuniary (non-specific)**: I hold the shares with Astrazeneca and GlaxoSmithKleine.	As Astrazeneca nor GlaxoSmithKleine is involved in the manufacture of any products relevant to the varicose vein guideline AD, NO'F and KK agreed that no action is necessary.
Fourth GDG Meeting [25/01/12]	No change to declarations of interest.	None
Fifth GDG Meeting [07/03/12]	No change to declarations of interest.	None
Sixth GDG Meeting [18/04/12]	No change to declarations of interest.	None
Seventh GDG Meeting [11/07/12]	No change to declarations of interest.	None
Eighth GDG Meeting [03/10/12]	No change to declarations of interest.	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	No change to declarations of interest.	None
Eleventh GDG Meeting [10/04/13]		

B.7 Mr Nick Hickey

GDG meeting	Declaration of Interests	Action taken
On Application	Personal pecuniary interest - I am employed by the NHS as a vascular surgeon, the role includes the management of varicose veins. I am also in private practice, including the treatment of varicose veins.	No action necessary
First GDG meeting [21/09/11]	No change to declarations of interest.	None
Second GDG	No change to declarations of interest.	None

GDG meeting	Declaration of Interests	Action taken
Meeting [02/11/11]		
Third GDG Meeting [14/12/11]	No change to declarations of interest.	None
Fourth GDG Meeting [25/01/12]	No change to declarations of interest.	None
Fifth GDG Meeting [07/03/12]	No change to declarations of interest.	None
Sixth GDG Meeting [18/04/12]	No change to declarations of interest.	None
Seventh GDG Meeting [11/07/12]	No change to declarations of interest.	None
Eighth GDG Meeting [03/10/12]	No change to declarations of interest.	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	No change to declarations of interest.	None
Eleventh GDG Meeting [10/04/13]		

B.8 Mr Keith Poskitt

GDG meeting	Declaration of Interests	Action taken
On Application	KP declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None

GDG meeting	Declaration of Interests	Action taken
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	**Personal pecuniary (non-specific):** Attendance at Veith Symposium meeting	No direct sponsorship by any manufacturer company involved in varicose veins related products. Funding not beyond that reasonably expected. AD, NOF and KK agreed no action was necessary.
Fourth GDG Meeting [25/01/12]	None	None
Fifth GDG Meeting [07/03/12]	**Personal non pecuniary**: Attended a breakfast meeting on chronic venous insufficiency at House of Commons on 7th March 2012	AD, NOF and KK agreed that no action was necessary.
Sixth GDG Meeting [18/04/12]	None	None
Seventh GDG Meeting [11/07/12]	**Non personal pecuniary (specific):** Received funding from STD pharmaceuticals to support a trip by his registrar to present research in Florence at European Venous Forum	KK and KH agreed that no action was necessary.
Eighth GDG Meeting [03/10/12]	No change to declarations of interest.	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	No change to declarations of interest.	None
Eleventh GDG Meeting [10/04/13]		

B.9 Ms. Hazel Trender

GDG meeting	Declaration of Interests	Action taken
On Application	HT declared she knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	**Personal pecuniary (specific):** Personal non-pecuniary - Sponsorship to attend Vascular Society Annual meeting from Medi UK	Medi-UK manufactures compression stocking which may be used for varicose veins patients. However, funding not beyond that reasonably expected. AD, NOF and KK agreed no action was necessary.
Fifth GDG Meeting [07/03/12]	No change to declarations of interest.	None
Sixth GDG Meeting [18/04/12]	**Personal pecuniary (specific):** Personal non-pecuniary - Funding for registration and accommodation for venous forum from Activa (stocking manufacturers)	Activa manufactures compressions stockings which may be used for varicose veins patients. However, funding not beyond that reasonably expected. AD, NOF and KK agreed no action was necessary.
Seventh GDG Meeting [11/07/12]	No change to declarations of interest.	None
Eighth GDG Meeting [03/10/12]	No change to declarations of interest.	None
Ninth GDG Meeting [07/11/12]	No change to declarations of interest.	None
Tenth GDG Meeting [19/12/12]	**Personal pecuniary (specific):** Sponsorship from Medi UK to attend the Vascular Society Meeting.	Medi-UK manufactures compression stocking which may be used for varicose veins patients. However, funding not beyond that reasonably expected. AD and KK agreed no action was necessary.
Eleventh GDG Meeting [10/04/13]		

B.10 Dr. Mark Vaughn

GDG meeting	Declaration of Interests	Action taken
On Application	MV declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	No action necessary
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	None	None
Fifth GDG Meeting [07/03/12]	None	None
Sixth GDG Meeting [18/04/12]	None	None
Seventh GDG Meeting [11/07/12]	None	None
Eighth GDG Meeting [03/10/12]	None	None
Ninth GDG Meeting [07/11/12]	Did not attend this meeting	None
Tenth GDG Meeting [19/12/12]	**Personal non pecuniary**: Agreed to speak at the National Primary Care Conference in May 2013. There have been no discussions about payment.	None
Eleventh GDG Meeting [10/04/13]		None

B.11 Expert Advisors

B.11.1 Dr. Christine Evans

GDG meeting	Declaration of Interests	Action taken
On Application	None	None

B.11.2 Ms. Jenny Greenfield

GDG meeting	Declaration of Interests	Action taken
On application	None	None
First GDG meeting [21/09/11]	None	None
Second GDG Meeting [02/11/11]	None	None
Third GDG Meeting [14/12/11]	None	None
Fourth GDG Meeting [25/01/12]	None	None
Fifth GDG Meeting [07/03/12]	None	None
Sixth GDG Meeting [18/04/12]	Did not attend	None
Seventh GDG Meeting [11/07/12]	None	None
Eighth GDG Meeting [03/10/12]	Did not attend this meeting	None
Ninth GDG Meeting [07/11/12]	None	None

B.11.3 Ms. Janine Elson

GDG meeting	Declaration of Interests	Action taken
On application	None	None
Ninth GDG Meeting [07/11/12]	Did not attend this meeting	None

Appendix C: Review protocols

C.1 Chapter 5 – patient perceptions and expectations

Table 1: Review protocol: Patient perceptions and expectations

Review question	**What are the perceptions and expectations of people with varicose veins (e.g. natural history, treatment) and how can they be addressed?**
Objectives	• To identify the perceptions and expectations of people with varicose veins with regard to: ○ Risk factors for developing varicose veins ○ Progression of varicose veins ○ Expectations about treatment • To identify what information should be given to people with varicose veins in order to manage expectations and perceptions • To identify how information should be given
Setting	Primary and secondary care
Population	Adults with leg varicose veins.
Intervention	NA
Comparison	NA
Outcomes	Any perceptions and expectations that are identified by people with varicose veins about their condition including those before and after treatment. How people with varicose veins would like to receive information on their condition.
Evaluation	Narrative summary of findings on patient perceptions and expectations related to the assessment, treatment, treatment success/failure, retreatment, adverse events and disease progression of varicose veins. Studies suggesting how such expectations can be addressed were also evaluated.
Exclusion	Studies that do not specify a varicose veins population. Opinion papers
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL and Psych Lit. Studies will be restricted to English language only. We will look for studies collecting data on patient expectations and perceptions related to the assessment, treatment, treatment success/failure, retreatment, adverse events and disease progression of varicose veins including risk factors for development of varicose veins. We will also look for studies suggesting how such expectations can be addressed.
The review strategy	Qualitative studies and questionnaire surveys will be searched If there are no published opinions on how expectations can be addressed, that part of the question will be answered solely by GDG consensus.
Key papers	Shepherd AC et al. Phlebology 2010; 25: 54-65 Darvall KA et al. Euro J Vasc Endovasc Surg 2009; 38: 642-647 Palfreyman SJ et al. J Clin Nurs 2004; 13: 332-340

C.2 Chapter 6 – referral to a vascular service

C.2.1 Factors associated with disease progression

Table 2: Review protocol: factors associated with disease progression

Review question	**a. In people with leg varicose veins at CEAP class C2 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C3, ii) C4*, iii) C6?** **b. In people with leg varicose veins at CEAP class C3 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C4*, ii) C6?** **c. In people with leg varicose veins at CEAP class C4* which signs, symptoms and/or patient characteristics are associated with disease progression to C6?** *** Will separate out CEAP classes C4a and C4b where evidence exists**
Population	Adults with leg varicose veins at CEAP stage C2 OR C3 OR C4 [as in parts a), b) and c) of the clinical question]
Prognostic Factors	Clinical signs that can be assessed prior to referral to a vascular service: • Location/extent of varicose veins • Any other aspects of physical examination Clinical symptoms that can be assessed prior to referral to a vascular service: • Severity of pain • Severity of other varicose veins symptoms Patient characteristics that can be assessed prior to referral to a vascular service: • Age • BMI • Comorbidities • Pregnancy/no of previous pregnancies • Severity of pain • Severity of other varicose veins symptoms • Past history of deep vein thrombosis (DVT) • Recurrent varicose veins
Outcomes	Progression to the CEAP class endpoints defined by parts a), b) or c) of the clinical question
Exclusion	Studies that do not specify a varicose veins population. • Stratify studies with people who have previously-treated varicose veins • Exclude studies where follow-up was less than 1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Studies will be restricted to English Language only
The review strategy	Where studies based on individual patient data (pooled analysis) are available, these are reviewed and other type of evidence such as meta-analysis, systematic reviews, prospective cohorts/case-control and cross-sectional studies are not included. Hierarchy of evidence (only go down a level if there is a lack of evidence): • Pooled analysis of patient level data • Meta-analysis/systematic reviews • Cohort Studies • Other observational studies
Key papers	Bonn vein studies, Nelson, NZ data, Framingham study

C.2.2 Factors associated with treatment success

Table 3: Review protocol: factors associated with treatment success

Review question	**In people with leg varicose veins are there any factors (clinical signs and symptoms or patient reported outcomes) that would predict increased benefits or harms from varicose veins interventional treatments?**
Population	Adults with leg varicose veins
Prognostic Factors	Clinical signs and symptoms that can be assessed prior to referral to a vascular service: • Any aspects of physical examination (CEAP) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis, swelling (oedema), aching, heaviness.) Patient characteristics that can be assessed prior to referral to a vascular service: • Age • BMI • Comorbidities • Parity • Recurrent varicose veins • Medical history (including family history) Patient reported outcomes that can be assessed prior to referral to a vascular service: • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) • disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score).
Outcomes	**Patient-reported outcome**:- • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score). • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score, CEAP) **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention** (including venous thrombo-embolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); major neurological event (i.e. stroke); local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; post-procedure pain; phlebitis; skin pigmentation/discolouration.

Review question	**In people with leg varicose veins are there any factors (clinical signs and symptoms or patient reported outcomes) that would predict increased benefits or harms from varicose veins interventional treatments?**
	Prevention of complications from varicose veins (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work/normal activities**
Exclusion	Studies that do not specify a varicose veins population. Studies not using a multivariable analysis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Studies will be restricted to English Language only
The review strategy	Where studies based on individual patient data (pooled analysis) are available, these are reviewed and other type of evidence such as meta-analysis, systematic reviews, prospective cohorts/case-control and cross-sectional studies are not included. Hierarchy of evidence (only go down a level if there is a lack of literature): • Pooled analysis of patient level data • Meta-analysis/systematic reviews • Cohort Studies • Other observational studies
Analysis	Stratification will occur by treatment type.

C.3 Chapter 7 – assessment for treatment

C.3.1 Diagnostic accuracy of hand held Doppler

Table 4: Review protocol: Diagnostic accuracy of hand held Doppler

Review question	**What is the diagnostic accuracy of hand held Doppler (HHD) compared to Duplex scanning when used in patients with varicose veins?**
Population	Adults with leg varicose veins.
Index tests	Hand held Doppler ultrasound testing for venous reflux
Reference standard	Duplex ultrasound scanning for venous reflux
Outcomes	**Main outcomes:** • Sensitivity (%) and specificity (%), for particular threshold(s) • Area under the ROC curve (AUC) – measure of predictive accuracy **Other outcomes:** • Positive/negative predictive value • Positive/ negative diagnostic likelihood ratios • Post-test probability (at a set pre-test probability)
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	Diagnostic studies
Analysis	We will analyse the diagnostic accuracy of hand held Doppler ultrasound. We will note at what point in the patient pathway the study is done.

C.3.2 Assessment with duplex prior to interventional treatment

Table 5: Review protocol: Duplex vs. no duplex prior to interventional treatment

Review question	**Does the use of duplex ultrasound during assessment improve outcome after interventional treatment compared to no duplex scanning in people with leg varicose veins?**
Population	Adults with leg varicose veins.
Intervention	Duplex ultrasound assessment prior to interventional treatment (surgery, endothermal ablation or foam sclerotherapy)
Comparison	No duplex ultrasound assessment prior to interventional treatment
Outcomes	**Patient-reported outcome:-** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score) <N.B. to use overall scores only> • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis, swelling, aching, heaviness). **Physician-reported outcomes** (venous clinical severity score or venous disability score). <N.B. to use overall scores only> **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years *<N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis>* **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention** including: • venous thromboembolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); • major neurological event (i.e. stroke); • local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis; • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work/normal activities**
Exclusion	Studies that do not specify a varicose veins population. Studies that compare different interventions as well as the use/no use of duplex
Search	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL.

Review question	**Does the use of duplex ultrasound during assessment improve outcome after interventional treatment compared to no duplex scanning in people with leg varicose veins?**
strategy	Studies will be restricted to English language only.
The review strategy	Systematic reviews RCTs Non-randomised clinical trials
Analysis	We should stratify by the different interventional treatments used in the different studies, as the difference between use of duplex and no duplex may differ depending on which treatment is subsequently used (for example, the use of duplex may be important in optimising surgical outcomes, but may be less important with thermal ablation). Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by primary and recurrent varicose veins.

C.4 Chapter 8 – conservative management

C.4.1 Conservative treatment vs. no treatment

Table 6: Review protocol: compression vs. no treatment/lifestyle advice

Review question	What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins?
Population	Adults with varicose veins in the legs
Intervention	Compression therapy, specifically compression hosiery (compression stockings) Both above knee and below knee compression hosiery will be included. [There will be no comparison between types of compression therapy].
Comparison	• no treatment, or • non-compressive stockings, or • placebo, or • lifestyle advice (including advice on weight loss, exercise, smoking, occupational standing/leg elevation, etc.)
Outcomes	**Patient-reported outcome** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score). • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body image, swelling (oedema), aching, heaviness.) **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: • Immediate: ≤1 month post intervention • Intermediate: >1month up to 12 months post intervention • Long term: >12 months up to 5 years post intervention **Adverse events from intervention** including: • manifestations of reduced arterial flow, • skin pressure damage • ulceration, • allergic reactions, • blistering, discomfort, • a sensation of excessive tightness. • Also non-compliance, and withdrawal from study due to adverse effects **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis.
Exclusion	Compression therapy applied after an interventional procedure (i.e. after sclerotherapy). Compression or bandaging applied for the management of venous ulcers (i.e. C6) Pneumatic intermittent compression. Studies that do not specify a varicose veins population

Review question	**What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins?**
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only
Search terms	Elastic stockings (graduated) Compression therapy/hosiery/stockings
The review strategy	Systematic reviews RCTs (cross over trials will be included where the time of treatment was short enough not to result in a natural change in patient condition and the washout period long enough to negate any impact of the stockings). If no RCTs, then conference abstracts, and then observational studies.
Analysis	Stratification for studies focussed on pregnant women. A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results: Sub-group for disease stage (i.e. CEAP classification, C2, C3, C4, C5). Sub group for above and below knee hosiery

C.4.2 Compression vs. interventional treatment

Table 7: Review protocol: compression vs. interventional treatment

Review question	**What is the clinical and cost effectiveness of compression therapy compared with** **a) stripping surgery; or** **b) endothermal ablation; or** **c) foam sclerotherapy** **in people with leg varicose veins?**
Population	Adults with varicose veins in the legs
Intervention	Compression therapy, specifically compression hosiery (compression stockings) Both above knee and below knee compression hosiery will be included. [There will be no comparison between types of compression therapy].
Comparison	Foam sclerotherapy ± crossectomy OR Stripping surgery + ligation [± phlebectomy] OR Endothermal ablation [± foam sclerotherapy/phlebectomy]
Outcomes	**Patient-reported outcomes** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score). • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body image, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: • Immediate: ≤1 month post intervention • Intermediate: >1month up to 12 months post intervention • Long term: >12 months up to 5 years post intervention **Adverse events from intervention** including: • manifestations of reduced arterial flow, • major vascular injury, • skin pressure damage, • ulceration, • allergic reactions, • blistering, • discomfort, • sensation of excessive tightness. • venous thromboembolism (pulmonary embolism [PE] and deep vein thrombosis (DVT); • Central neurological event (permanent (i.e. stroke, TIA) and transient i.e. migraine, transient visual disturbance); • local neurological events (permanent and transient) i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis;

Review question	**What is the clinical and cost effectiveness of compression therapy compared with** **a) stripping surgery; or** **b) endothermal ablation; or** **c) foam sclerotherapy** **in people with leg varicose veins?**
	• skin pigmentation/discolouration. • Also non-compliance, and withdrawal from study due to adverse effects) **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work and/or normal activities**
Exclusion	Studies that do not specify a varicose veins population Compression therapy applied after an interventional procedure (i.e. after sclerotherapy). Compression or bandaging applied for the management of venous ulcers (i.e. C6) Pneumatic intermittent compression. Cryostripping
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only
The review strategy	RCTs first. If no RCTs, then conference abstracts, and then observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Stratification for studies focussed on pregnant women. Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results: Sub-group for disease stage (i.e. CEAP classification, C2, C3, C4, C5). Sub group for above and below knee hosiery

C.5 Chapter 9 – interventional treatment

C.5.1 Stripping surgery vs. foam sclerotherapy

Table 8: Review protocol: Stripping surgery vs. foam sclerotherapy

Review question	**What is the clinical and cost effectiveness of stripping surgery compared with foam sclerotherapy in people with truncal leg varicose veins?**
Population	Adults with truncal leg varicose veins.
Intervention	Stripping surgery (including conventional stripping, invagination stripping=inverting stripping=PIN [perforation invagination], 'high-tie'=crossectomy, saphenofemoral junction disconnection, saphenopopliteal) with ligation, sequential stripping surgery. [± phlebectomy] [NOTE: Stripping surgery comes hand-in-hand with ligation, i.e. it is normal practice for ligation to occur before stripping]
Comparison	Foam sclerotherapy [± crossectomy (ligation)] [NOTE: compression therapy is applied after the procedure as part of the treatment]
Outcomes	**Patient-reported outcome**:- • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score). • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body language, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years **<N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis>** **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention** including: • venous thrombo-embolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); • major neurological event (i.e. stroke); • local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis; • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis.

	Return to work/normal activities
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	RCTs first. If no RCTs are available, then consider conference abstracts, and if none are available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Stratification from the outset: • foam sclerotherapy ± crossectomy (i.e. ligation). • primary and recurrent varicose veins Further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6).
Key papers	Murad MH, Coto-Yglesias F, Zumaeta-Garcia M, Elamin MB, Duggirala MK, Erwin PJ, Montori VM, and Gloviczki P. A systematic review and meta-analysis of the treatments of varicose veins. [Review]. Journal of Vascular Surgery 2011; 53: 49S - 65S Rigby KA, Palfreyman SJ, Beverley C, Michaels JA. Surgery versus sclerotherapy for the treatment of varicose veins. Cochrane Database Syst Rev. 2004;18;(4):CD004980.

C.5.2 Stripping surgery vs. endothermal ablation

Table 9: Review protocol: stripping surgery vs. endothermal ablation

Review question	**What is the clinical and cost effectiveness of stripping surgery compared with endothermal ablation in people with truncal leg varicose veins?**
Population	Adults with truncal leg varicose veins.
Intervention	Stripping surgery (including conventional stripping, invagination stripping=inverting stripping=PIN [perforation invagination], 'high-tie'=crossectomy, saphenofemoral junction disconnection, saphenopopliteal) with ligation, sequential stripping surgery. [± phlebectomy] [NOTE: Stripping surgery comes hand-in-hand with ligation, i.e. it is normal practice for ligation to occur before stripping]
Comparison	Endothermal ablation, including: • radiofrequency ablation • (endovenous) laser ablation (EVLA) • steam ablation [± foam sclerotherapy/phlebectomy (for tributaries)]
Outcomes	**Patient-reported outcome**:- • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score). • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body language, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:**

Review question	**What is the clinical and cost effectiveness of stripping surgery compared with endothermal ablation in people with truncal leg varicose veins?**
	• Within 3 months • >3–12 months • >1–5 years **<N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis>** **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention** including: • venous thrombo-embolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); • major neurological event (i.e. stroke); • local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis; • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work/normal activities**
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	RCTs first. If no RCTs are available, then consider conference abstracts, and if none are available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Stratification from the outset: • primary and recurrent varicose veins Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by types of endothermal ablation
Key papers	van den Bos R, Arends L, Kockaert M, Neumann M, and Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. [Review] [42 refs]. Journal of Vascular Surgery 2009; 49: 230 - 239

C.5.3 Foam sclerotherapy vs. endothermal ablations

Table 10: Review protocol: foam sclerotherapy versus endothermal ablation

Review question	What is the clinical and cost effectiveness of foam sclerotherapy compared with endothermal ablation in people with truncal leg varicose veins?
Population	Adults with truncal leg varicose veins.
Intervention	Foam sclerotherapy(including ultrasound-guided foam sclerotherapy (UGFS)) [± crossectomy (ligation)] [NOTE: compression therapy is applied after the procedure as part of the treatment]
Comparison	Endothermal ablation, including: • radiofrequency ablation • (endovenous) laser ablation (EVLA) • steam ablation [foam sclerotherapy/phlebectomy (for tributaries)]
Outcomes	**Patient-reported outcome:-** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body image, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years **<N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis>** **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention** including: • venous thrombo-embolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); • major neurological event (i.e. stroke); • local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis; • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work/normal activities**

Review question	What is the clinical and cost effectiveness of foam sclerotherapy compared with endothermal ablation in people with truncal leg varicose veins?
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL.e Studies will be restricted to English language only.
The review strategy	RCTs first. If no RCTs are available, then consider conference abstracts of RCTs, and if none are available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Stratification from the outset: • foam sclerotherapy ± crossectomy (i.e. ligation). • primary and recurrent varicose veins Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by types of endothermal ablation.

C.5.4 Tributary treatment: avulsion surgery vs. foam sclerotherapy

Table 11: Review protocol: avulsion surgery vs. foam sclerotherapy for tributary treatment

Review question	What is the clinical and cost effectiveness of avulsion surgery compared with foam sclerotherapy in people with tributary leg varicose veins?
Population	Adults with tributary leg varicose veins.
Intervention	Avulsion surgery (ambulatory phlebectomy, phlebectomy)
Comparison	Foam sclerotherapy to tributary veins. (including ultrasound-guided foam sclerotherapy (UGFS)) [NOTE: compression therapy is applied after the procedure as part of the treatment]
Outcomes	**Patient-reported outcome:-** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/body image, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years <N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis> **Need for additional/further treatment (**i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention

Review question	**What is the clinical and cost effectiveness of avulsion surgery compared with foam sclerotherapy in people with tributary leg varicose veins?**
	• Long term: >1–5 years post intervention **Adverse events from intervention** including: • venous thrombo-embolism [VTE], i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT); • major neurological event (i.e. stroke); • local neurological events, i.e. nerve injury/damage, paraesthesia, neuralgia, numbness; • post-procedure pain; • phlebitis; • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work/normal activities**
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	RCTs first. If no RCTs are available, then consider conference abstracts, and if none are available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by primary and recurrent varicose veins.

C.5.5 Truncal treatment and tributary treatment vs. truncal treatment alone

Table 12: Review protocol: Truncal treatment and tributary treatment vs. truncal treatment alone

Review question	**What is the clinical and cost effectiveness of truncal treatment accompanied by tributary treatment (avulsion or sclerotherapy) compared with truncal treatment alone in people with leg varicose veins?**
Population	Adults with leg varicose veins.
Intervention	Stripping surgery[1] accompanied by tributary treatments (avulsion[2] / foam sclerotherapy[3]) OR Endothermal ablation[4] accompanied by tributary treatments (avulsion[2] / foam sclerotherapy[3]) OR Foam sclerotherapy[3] accompanied by tributary treatments (avulsion[2] / foam sclerotherapy[3]) 1: Stripping surgery (including conventional stripping, invagination stripping=inverting stripping=PIN [perforation invagination], ‘high-tie’=crossectomy, sapheno-femoral junction disconnection, sapheno-popliteal) with ligation, sequential stripping surgery.[± phlebectomy] 2: Avulsion surgery (ambulatory phlebectomy, phlebectomy)

Review question	**What is the clinical and cost effectiveness of truncal treatment accompanied by tributary treatment (avulsion or sclerotherapy) compared with truncal treatment alone in people with leg varicose veins?**
	3: Foam sclerotherapy 4: Endothermal ablation, including: radiofrequency ablation (endovenous) laser ablation (EVLA, EVLT) steam ablation [± foam sclerotherapy/phlebectomy (for tributaries)]
Comparison	The comparator in each case will be the truncal intervention, but without tributary treatment (avulsion / sclerotherapy) as an adjunct
Outcomes	**Patient-reported outcomes:-** • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis*, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years <N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis> **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention**, including: • venous thromboembolism (pulmonary embolism [PE] and deep vein thrombosis (DVT – to be reported separately) • global neurological event (i.e. stroke, TIA); • local neurological events (i.e. nerve injury/damage, paresthesia, neuralgia, numbness). • post-procedure pain • phlebitis • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis. **Return to work / normal activities**
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review	RCTs first. If no RCTs are available, then consider conference abstracts, and if none are

Review question	**What is the clinical and cost effectiveness of truncal treatment accompanied by tributary treatment (avulsion or sclerotherapy) compared with truncal treatment alone in people with leg varicose veins?**
strategy	available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Stratification from the outset: • foam sclerotherapy ± crossectomy (i.e. ligation). Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by primary and recurrent varicose veins.

C.6 Chapter 10 – compression after treatment

Table 13: Review protocol: compression after interventional treatment vs. interventional treatment alone

Review question	**What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins, and, if so, what type of compression, pressure of compression and/or duration of compression is optimal?**
Population	Adults with leg varicose veins.
Intervention	Stripping surgery[1] followed by compression[2] OR Avulsion surgery[3] followed by compression[2] OR Endothermal ablation[4] followed by compression[2] OR Foam sclerotherapy[5] followed by compression[2] 1: Stripping surgery (including conventional stripping, invagination stripping=inverting stripping=PIN [perforation invagination], 'high-tie'=crossectomy, saphenofemoral junction disconnection, saphenopopliteal) with ligation, sequential stripping surgery.[± phlebectomy]. Note: Short-term (up to 7 days) 'routine' elastic bandaging is allowed in both groups. 2: Compression therapy, specifically compression hosiery (compression stockings). Both above knee and below knee compression hosiery will be included. 3: Avulsion surgery (ambulatory phlebectomy, phlebectomy) Note: Short-term (up to 5 days) 'routine' elastic bandaging is allowed in both groups. 4: Endothermal ablation, including: • radiofrequency ablation • (endovenous) laser ablation (EVLA, EVLT) • steam ablation

Review question	**What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins, and, if so, what type of compression, pressure of compression and/or duration of compression is optimal?**
	[± foam sclerotherapy/phlebectomy (for tributaries)] Note: Short-term (up to 5 days) 'routine' elastic bandaging is allowed in both groups. 5: Foam sclerotherapy[± crossectomy (ligation)] Note: Short-term (up to 5 days) 'routine' elastic bandaging is allowed in both groups.
Comparison	For the first part of the review question, the comparator in each case will be as the intervention, but without compression as an adjunct. For the second part of the review question, the comparator will be as the intervention but adjunctive compression will vary in terms of: • another type of compression (i.e. bandaging) • a different compression pressure • a different duration of treatment
Outcomes	**Patient-reported outcome**:- • Health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) and disease specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis*, swelling (oedema), aching, heaviness. **Physician-reported outcomes** (venous clinical severity score or venous disability score). **Presence of reflux:** • Within 3 months • >3–12 months • >1–5 years **<N.B. if no reflux data is available, to include incomplete impartial occlusion/incomplete stripping rates within the same analysis>** **Need for additional/further treatment** (i.e. compression therapy and/or ablative techniques) over the following time periods: (same time intervals as above • Immediate: Within 3 months post intervention • Intermediate: >3–12 months post intervention • Long term: >1–5 years post intervention **Adverse events from intervention**, including: • venous thrombo-embolism (i.e. pulmonary embolism [PE] and deep vein thrombosis (DVT) – to be reported separately) • global neurological event (i.e. stroke); • local neurological events (i.e. nerve injury/damage, paresthesia, neuralgia, numbness). • post-procedure pain • phlebitis • skin pigmentation/discolouration. **Prevention of complications from varicose veins** (leg ulcer occurrence or recurrence, haemorrhage (bleeding) and thrombophlebitis.

Review question	**What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins, and, if so, what type of compression, pressure of compression and/or duration of compression is optimal?**
	Return to work / normal activities
Exclusion	Studies that do not specify a varicose veins population.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	RCTs first. If no RCTs are available, then consider conference abstracts, and if none are available then consider observational studies. Systematic reviews
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Sub-group by disease stage (i.e. CEAP classification C2, C3, C4, C5, C6). Sub-group by primary and recurrent varicose veins.

C.7 Economic review protocol

Table 14: Appended economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix F
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. **Inclusion/exclusion criteria** If a study is rated as both 'Directly applicable' and 'minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. If a study is rated as 'Partially applicable' and/or 'potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations[a] • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies: Setting: 1. UK NHS 2. OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) 3. OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) 4. Non-OECD settings (always 'Not applicable') Economic study type:

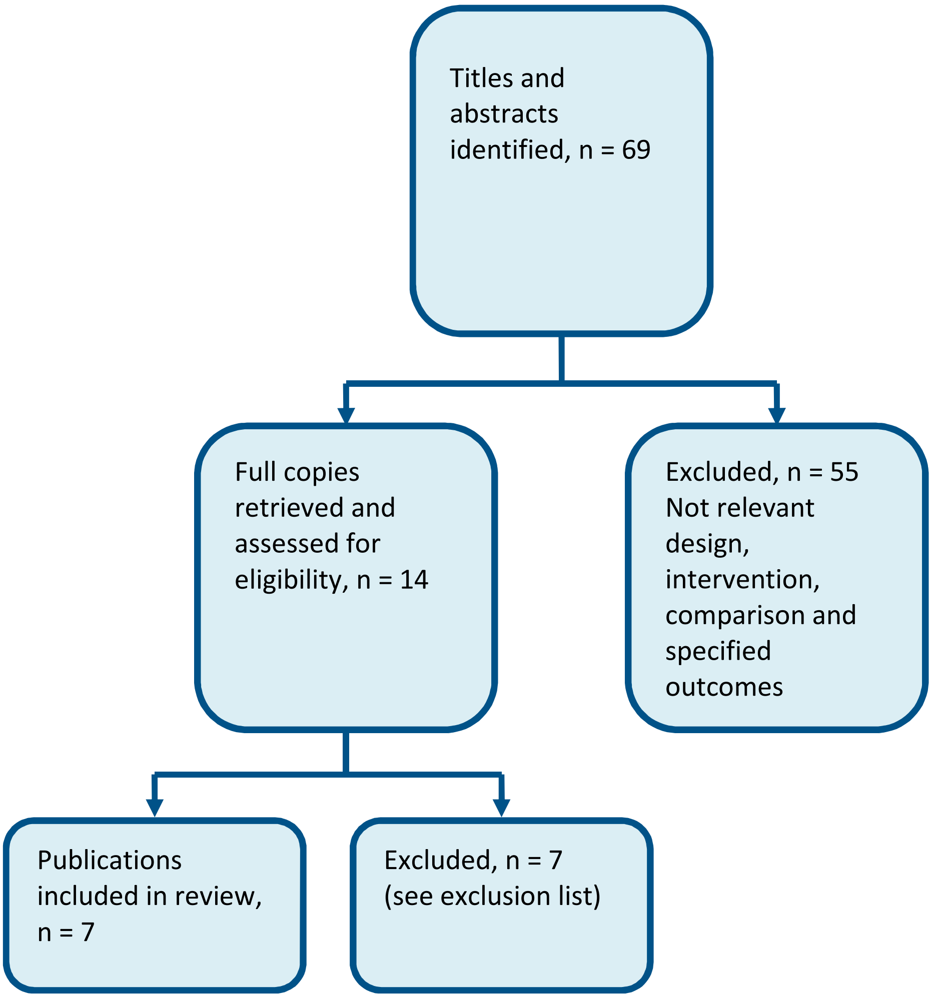
Review question	**All questions – health economic evidence**
	1. Cost-utility analysis 2. Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) 3. Comparative cost analysis 4. Non-comparative cost analyses including cost of illness studies (always 'Not applicable') Year of analysis: • The more recent the study, the more applicable it is Quality and relevance of effectiveness data used in the economic analysis: • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Clinical article selection

D.1 Chapter 5 – patient perceptions and expectations

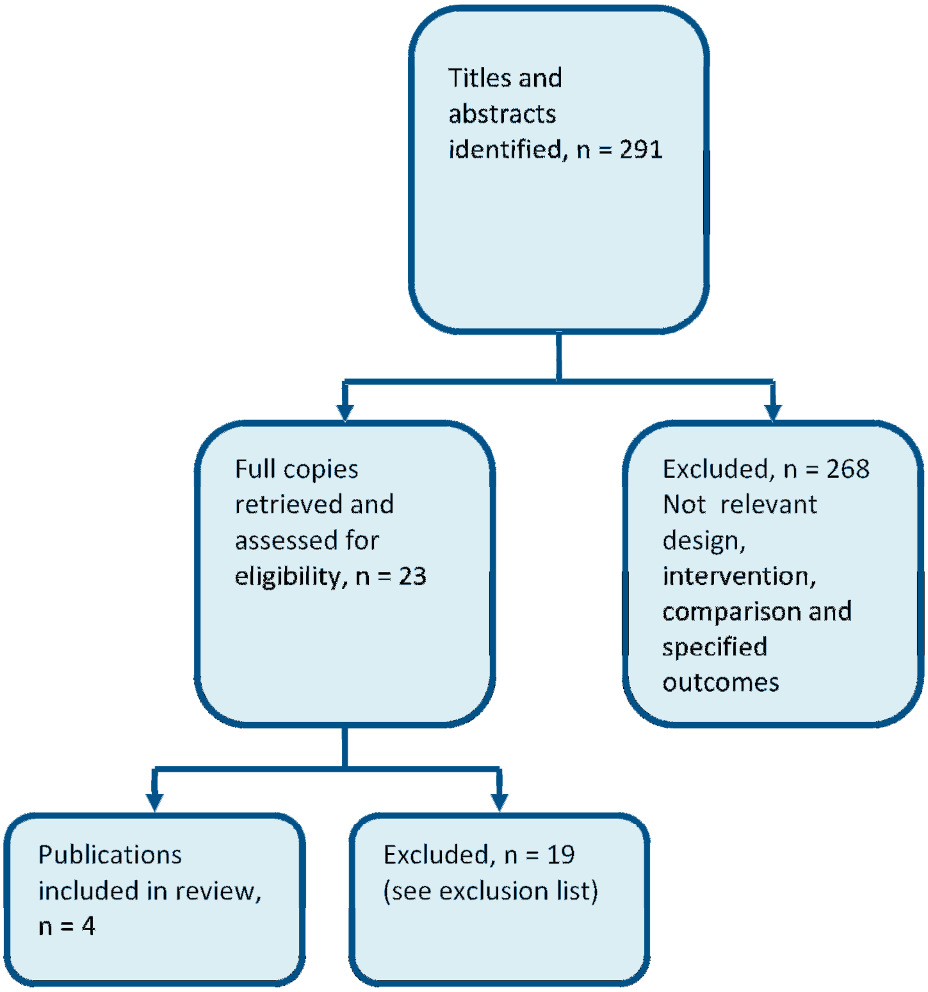
Figure 1: Clinical article selection: patient perceptions and expectations



D.2 Chapter 6 – referral to a vascular service

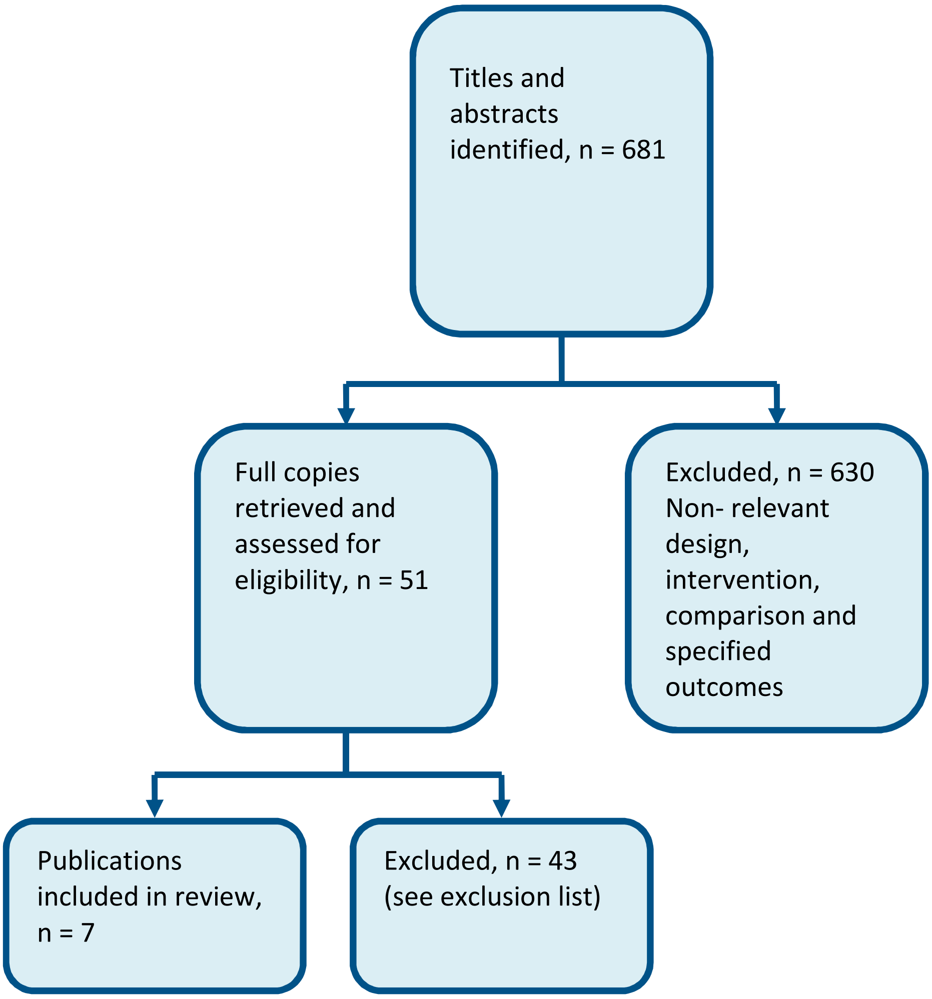
D.2.1 Risk factors associated with disease progression

Figure 2: Clinical article selection: factors associated with disease progression



D.2.2 Risk factors affecting treatment success

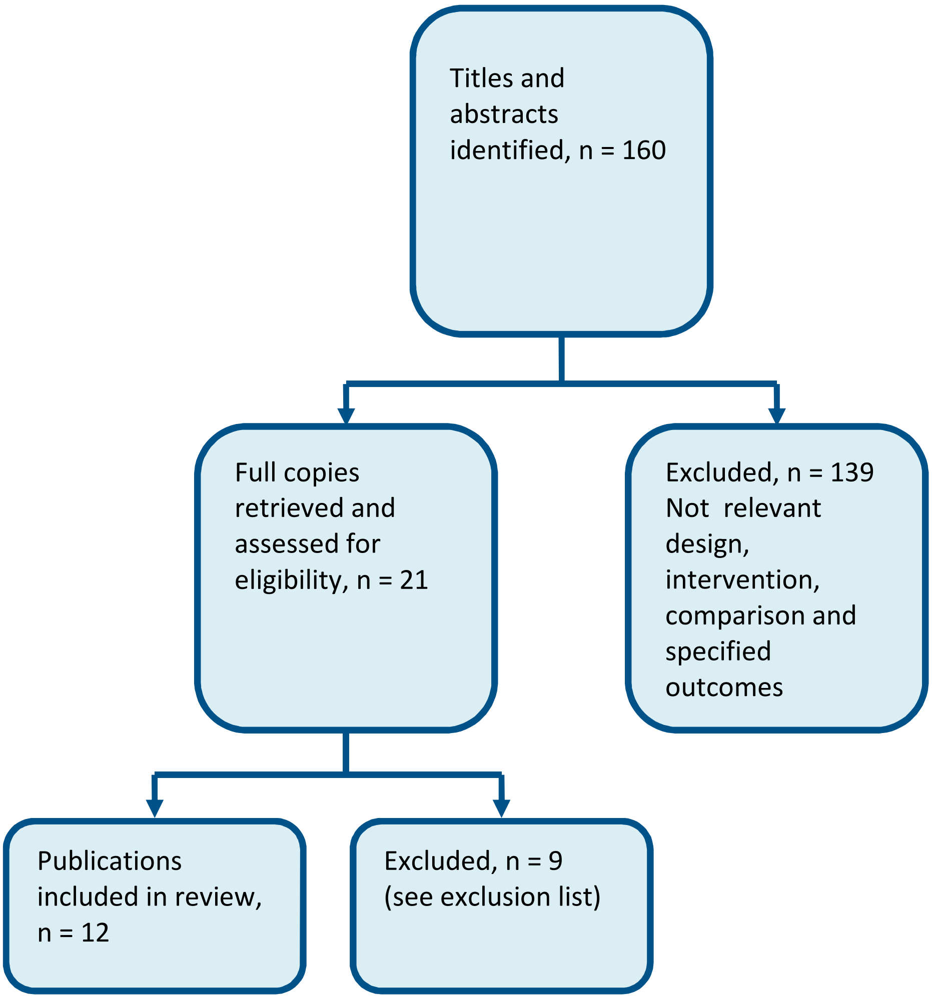
Figure 3: Clinical article selection: factors associated with treatment success/failure



D.3 Chapter 7 – assessment for treatment

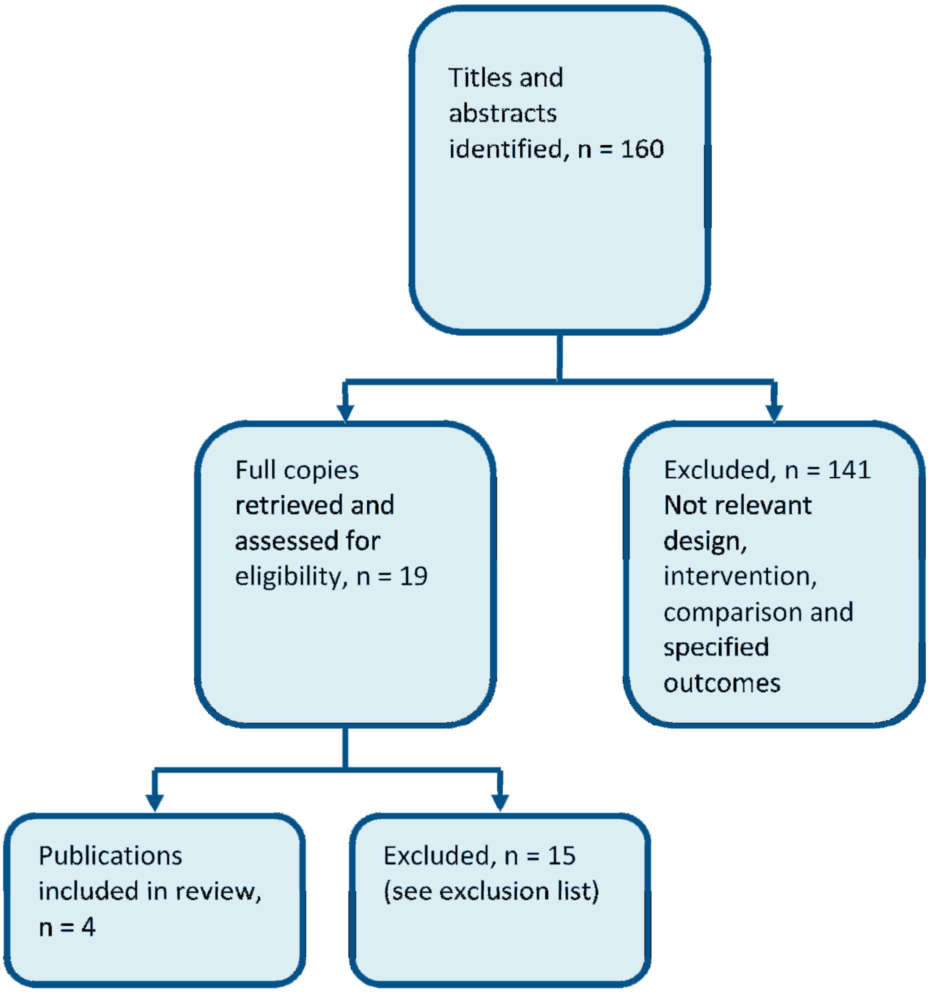
D.3.1 Diagnostic accuracy of hand held Doppler

Figure 4: Clinical article selection: diagnostic accuracy of hand held Doppler



D.3.2 Assessment with duplex prior to interventional treatment

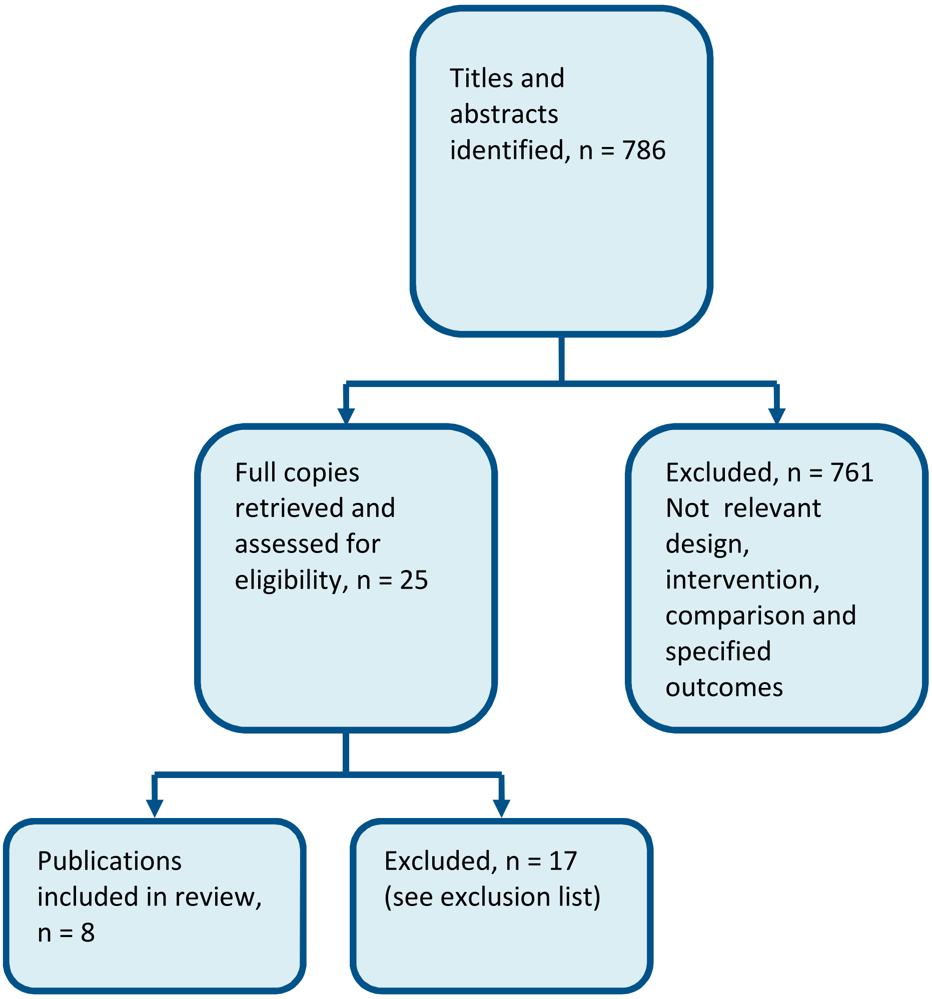
Figure 5: Clinical article selection: assessment with duplex prior to interventional treatment



D.4 Chapter 8 – conservative management

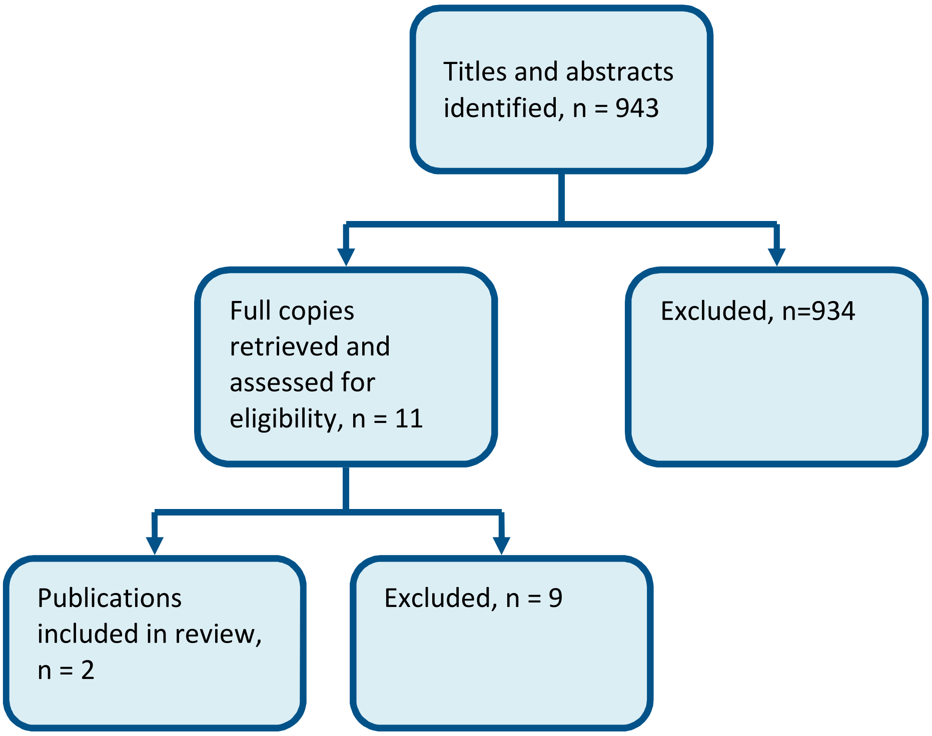
D.4.1 Compression vs. no treatment

Figure 6: Clinical article selection: compression vs. no treatment



D.4.2 Compression vs. interventional treatment

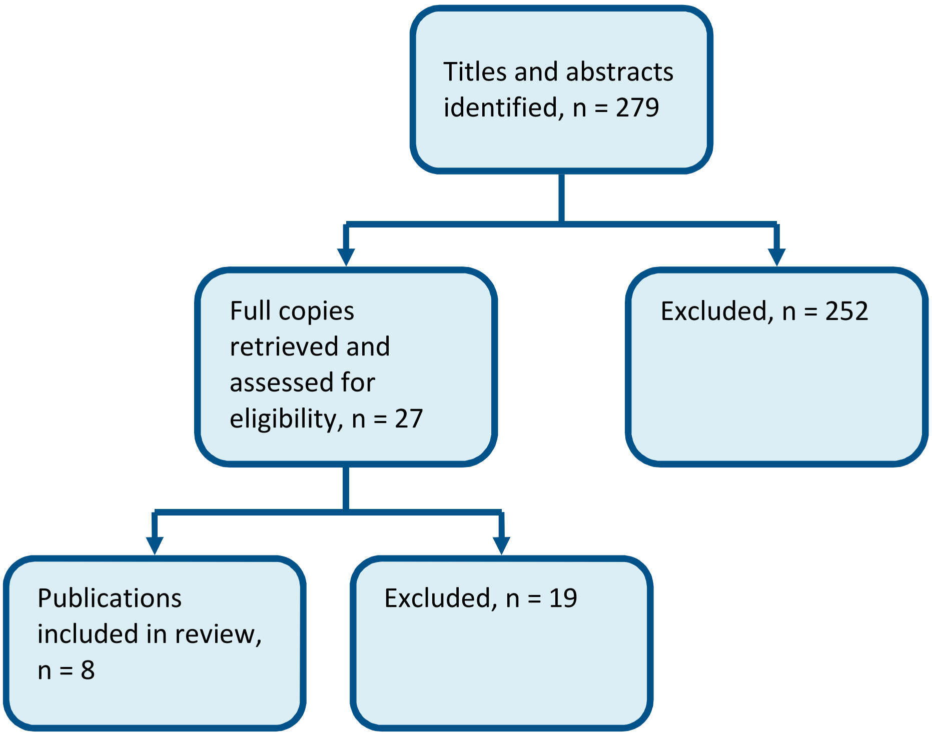
Figure 7: Clinical article selection for compression vs. interventional treatment



D.5 Chapter 9 – interventional treatment

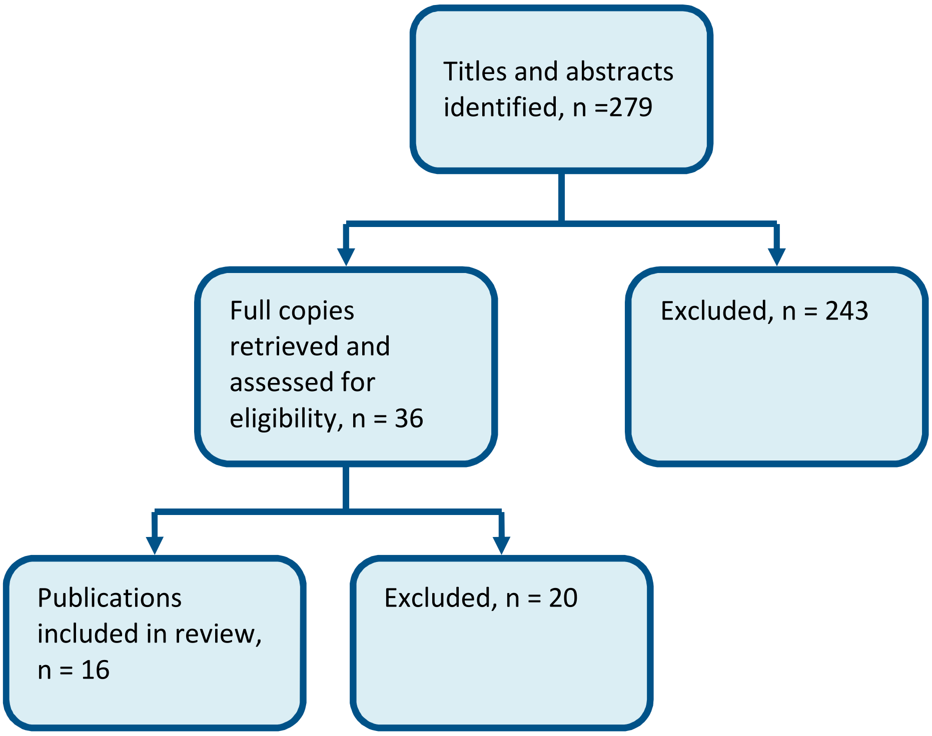
D.5.1 Stripping surgery vs. foam sclerotherapy

Figure 8: Clinical article selection: Stripping surgery vs. foam sclerotherapy review



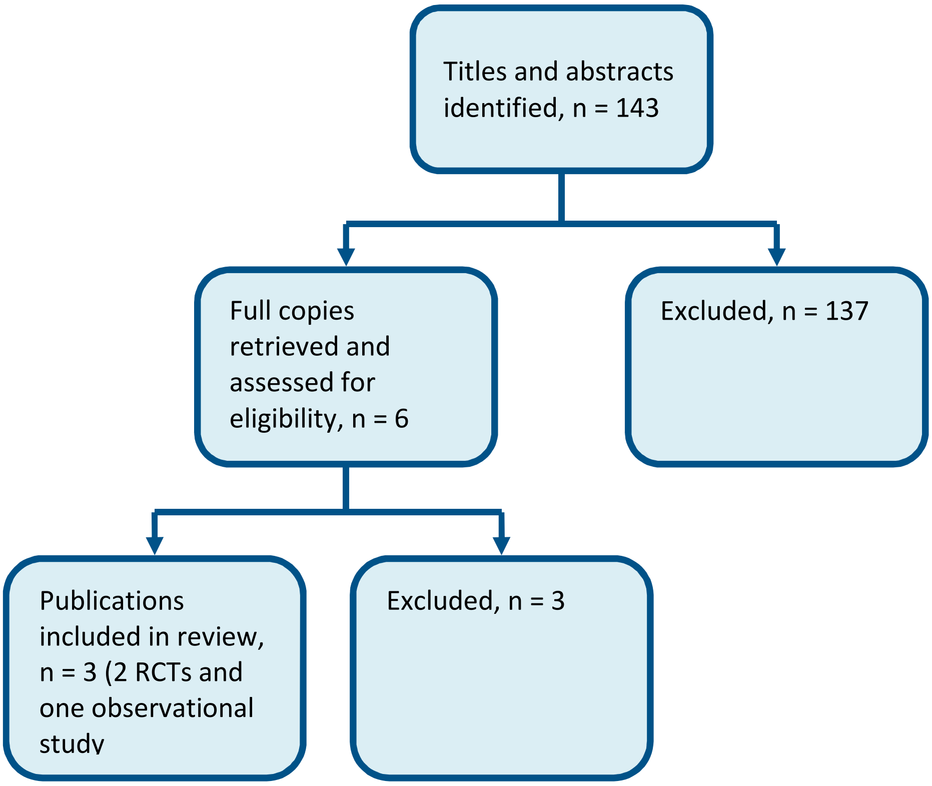
D.5.2 Stripping surgery vs. endothermal ablation

Figure 9: Clinical article selection: stripping surgery vs. endothermal ablation



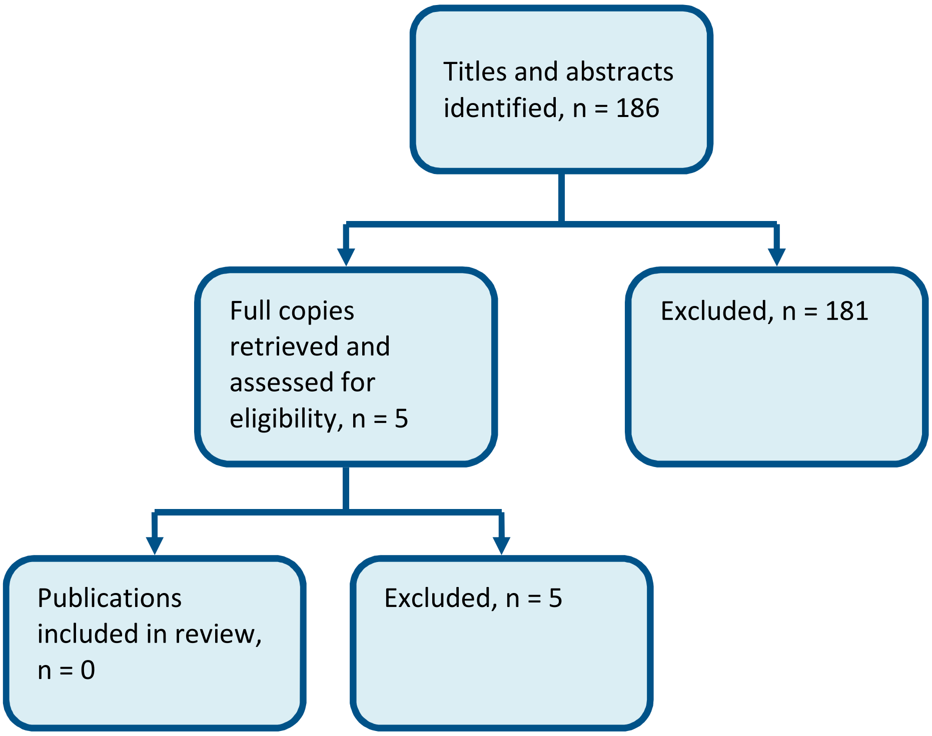
D.5.3 Foam sclerotherapy vs. endothermal ablation

Figure 10: Clinical article selection for foam sclerotherapy vs. endothermal ablation review



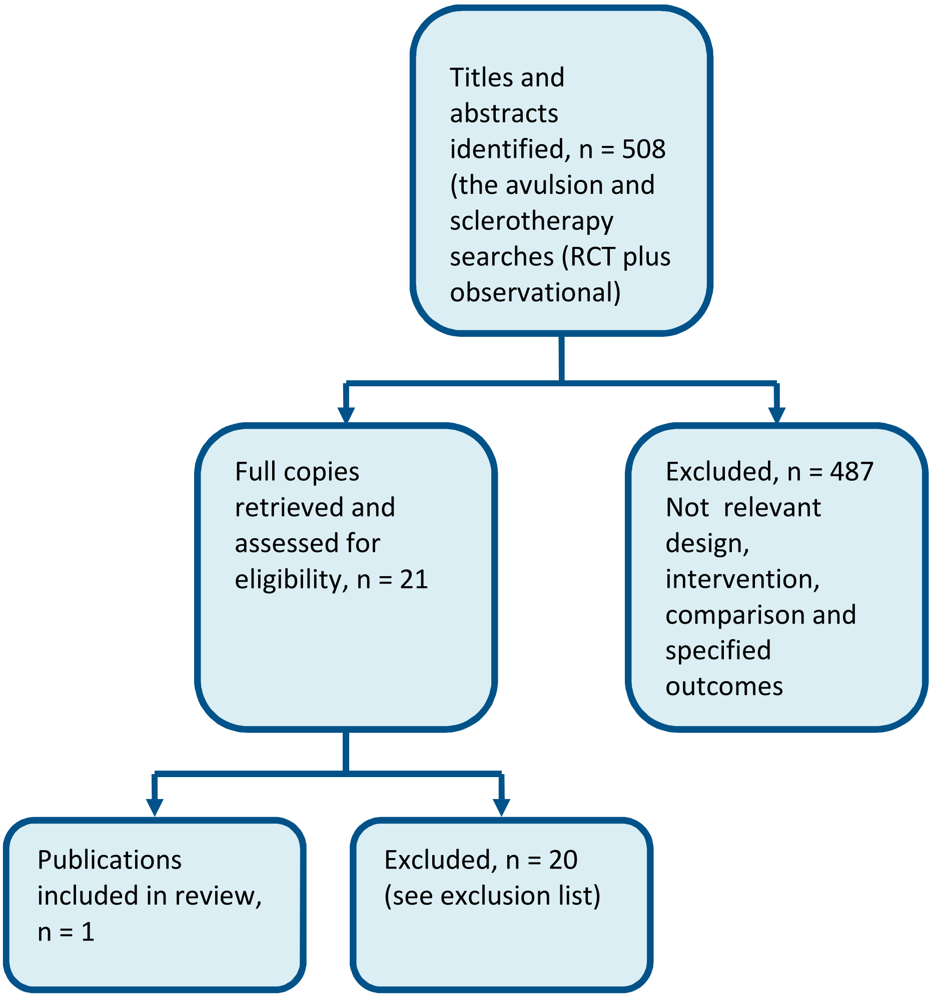
D.5.4 Tributary treatment: avulsion vs. foam sclerotherapy

Figure 11: Clinical article selection: foam sclerotherapy vs. avulsion for tributary veins



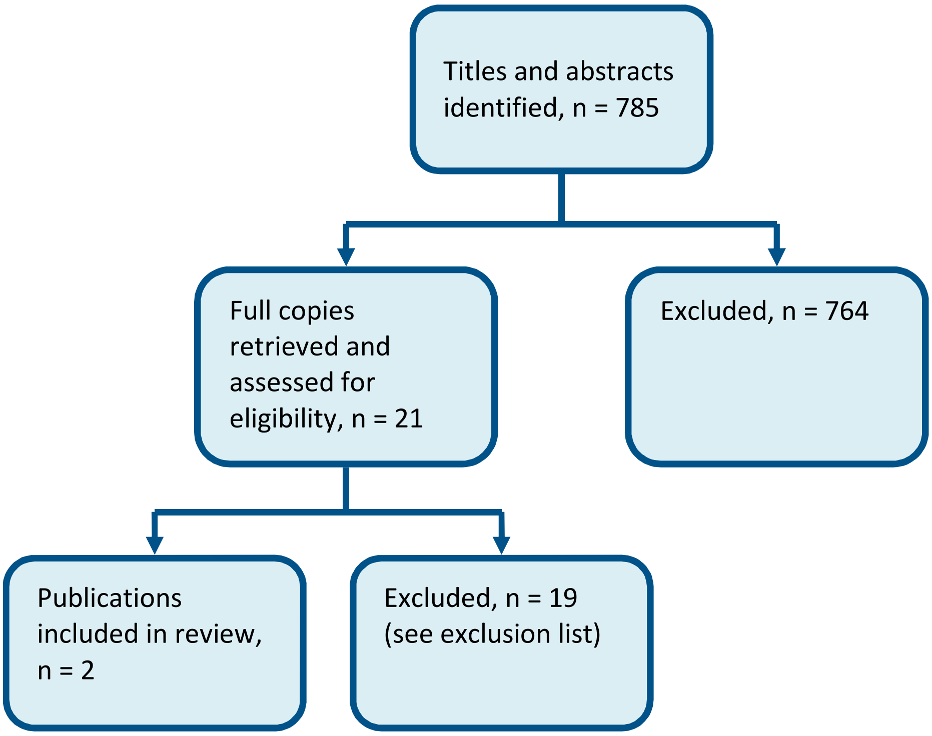
D.5.5 Truncal treatment and tributary treatment vs. truncal treatment alone

Figure 12: Clinical article selection: truncal with tributary treatment vs. truncal treatment alone



D.6 Chapter 10 – compression after interventional treatment

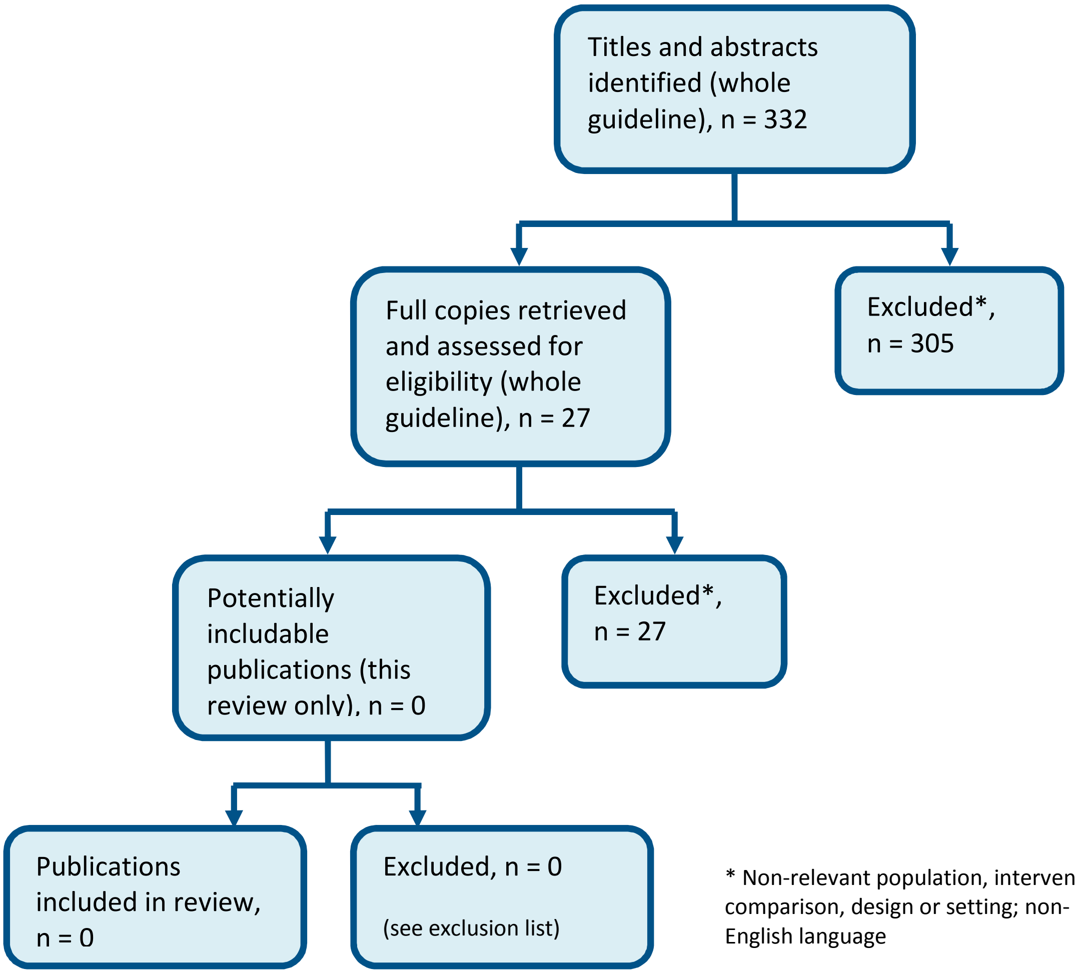
Figure 13: Clinical article selection: Interventional treatment with compression vs. interventional treatment alone



Appendix E: Economic article selection

E.1 Chapter 5 – patient perceptions and expectations

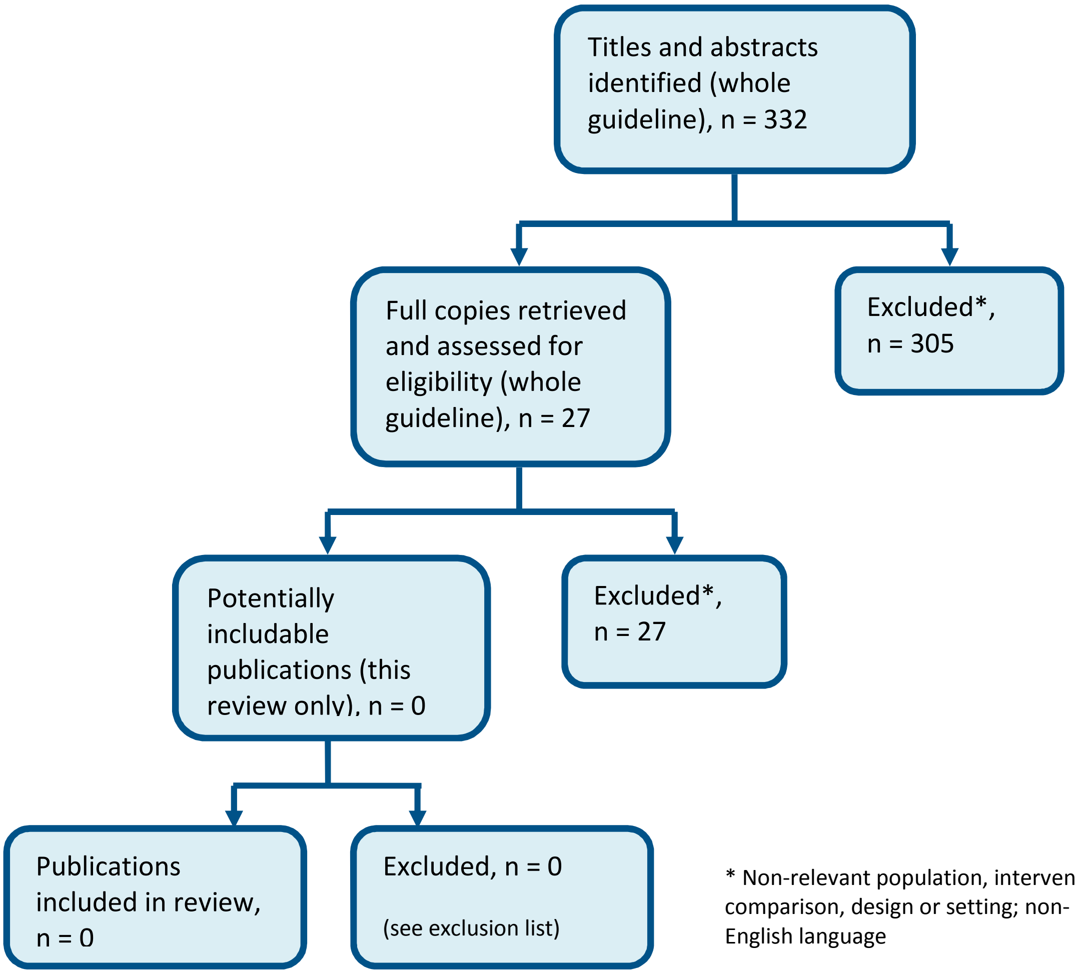
Figure 14: Economic article selection: patient perceptions and expectations



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.2 Chapter 6 – referral to a vascular service

Figure 15: Economic article selection: referral to a vascular service

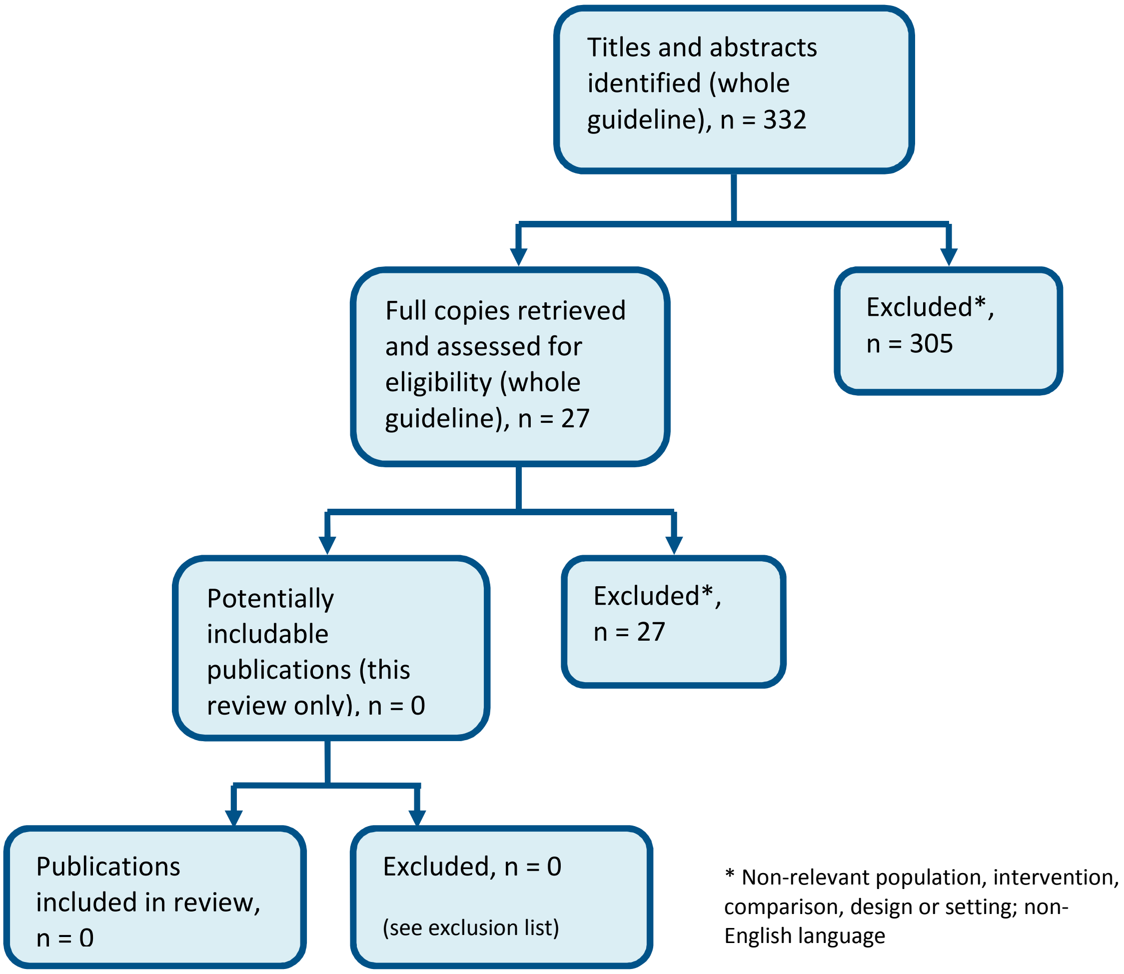


* Non-relevant population, intervention, comparison, design or setting; non-English language

E.3 Chapter 7 – assessment for treatment

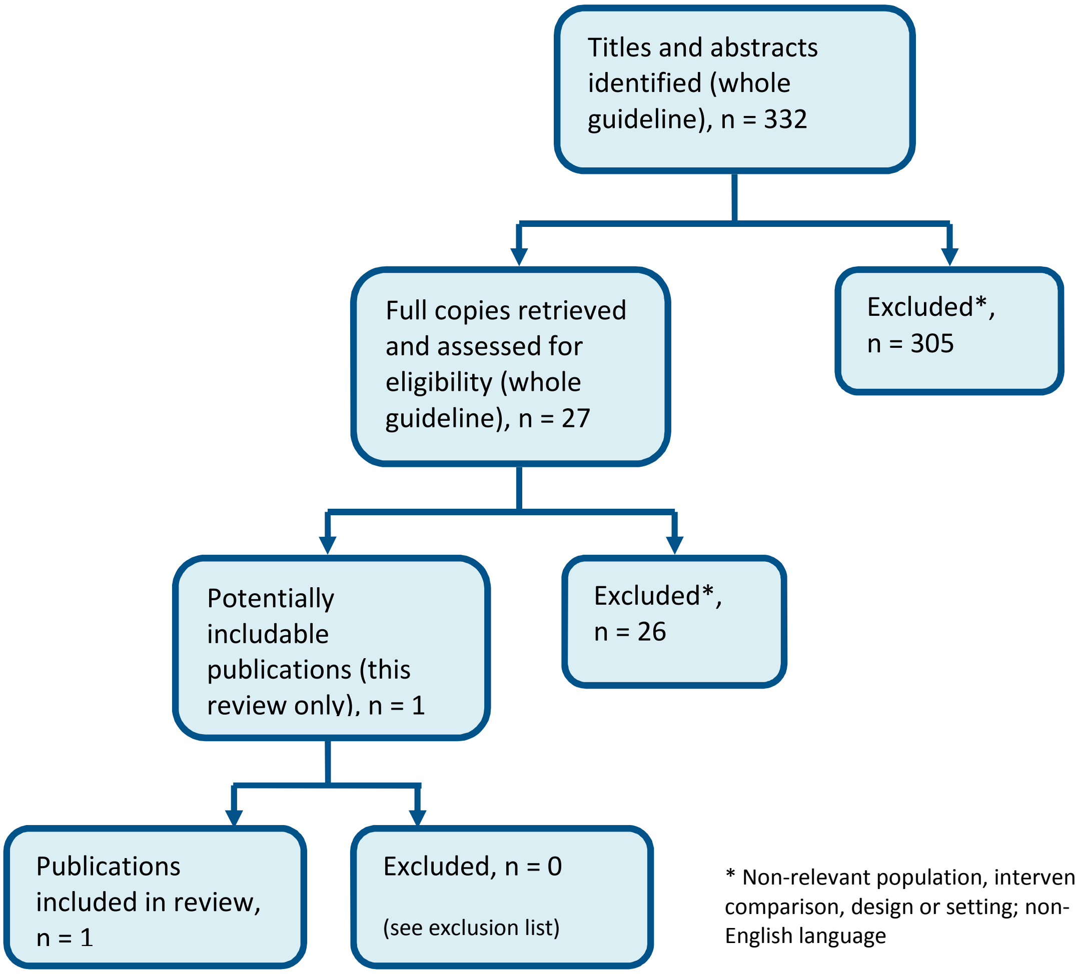
E.3.1 Duplex vs. Hand Held Doppler

Figure 16: Economic article selection: duplex vs. hand held doppler review



E.3.2 Duplex assessment prior to interventional treatment

Figure 17: Economic article selection: duplex assessment prior to interventional treatment

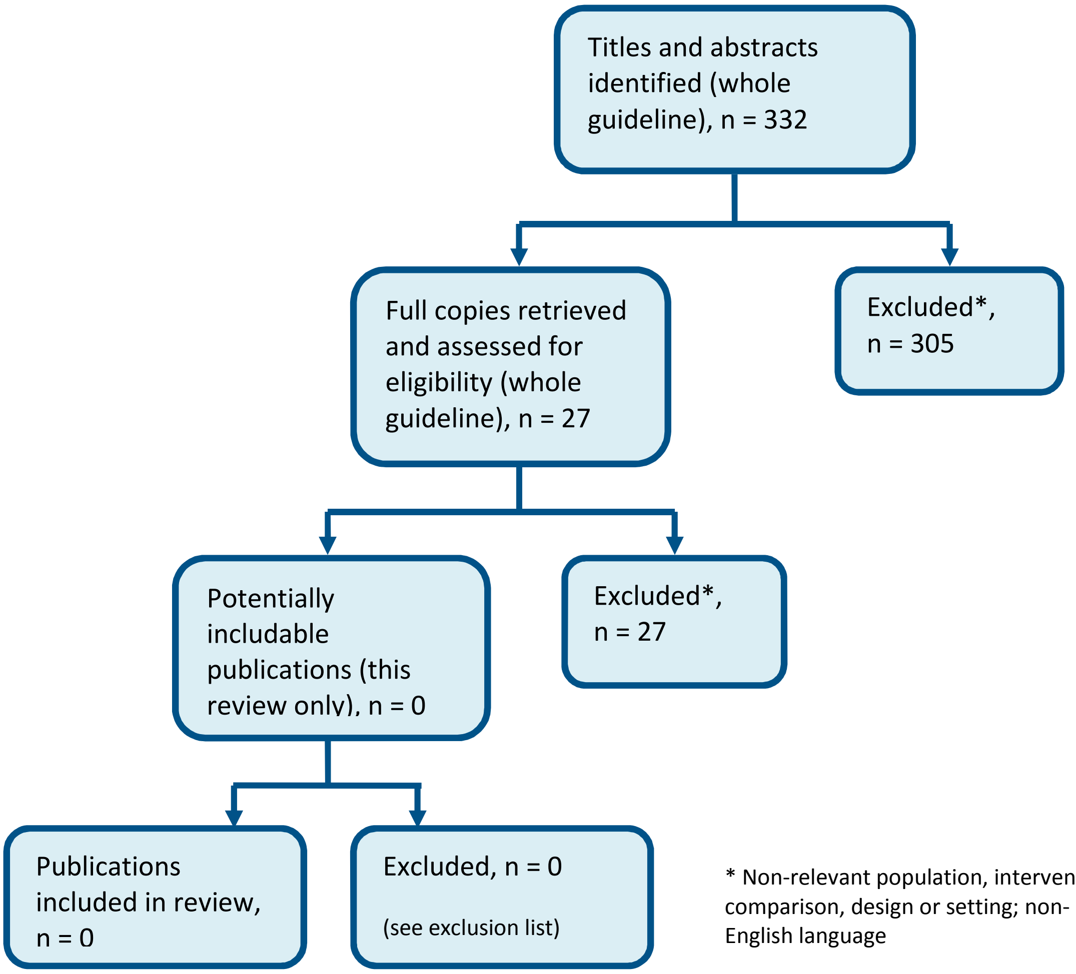


* Non-relevant population, intervention, comparison, design or setting; non-English language

E.4 Chapter 8 – conservative management

E.4.1 Compression vs. no treatment

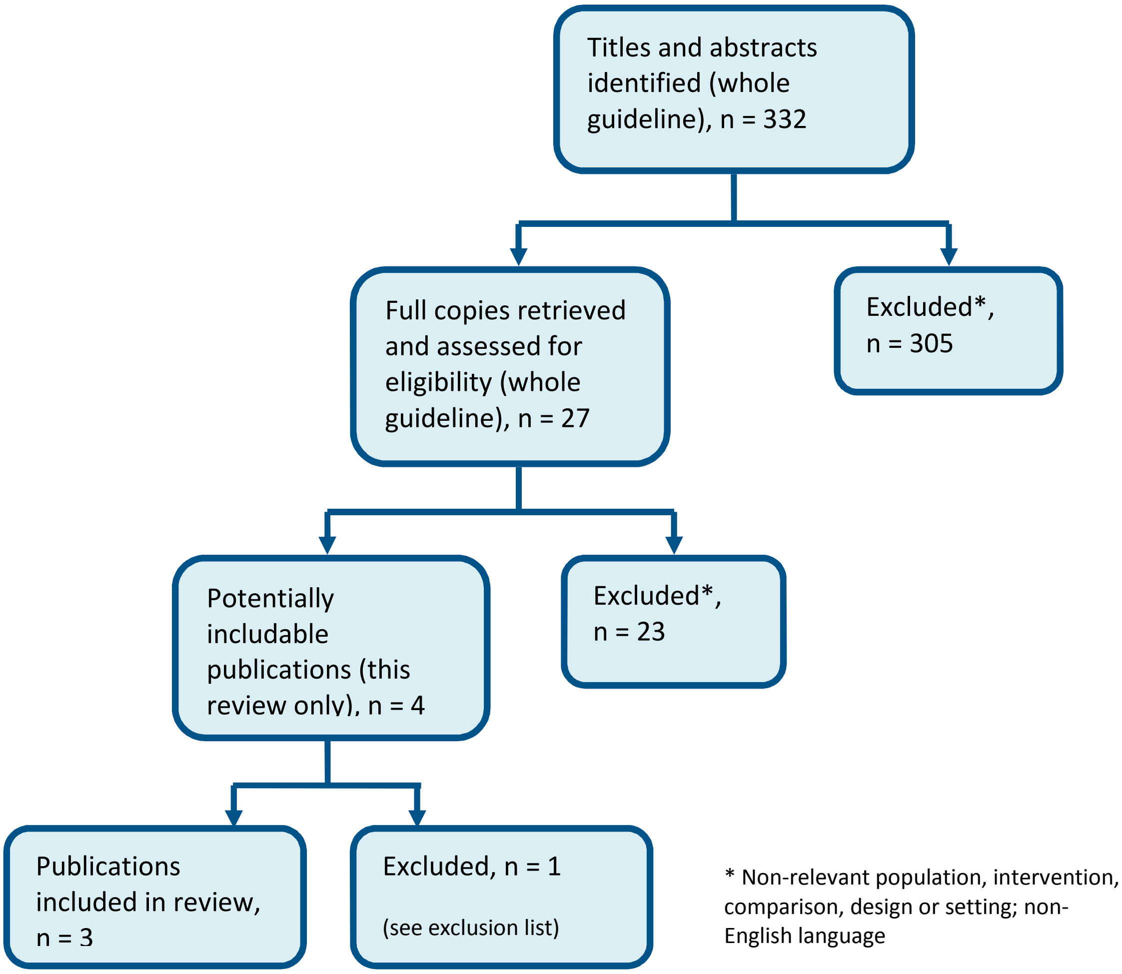
Figure 18: Economic article selection: compression vs.no treatment



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.4.2 Compression vs. interventional treatment

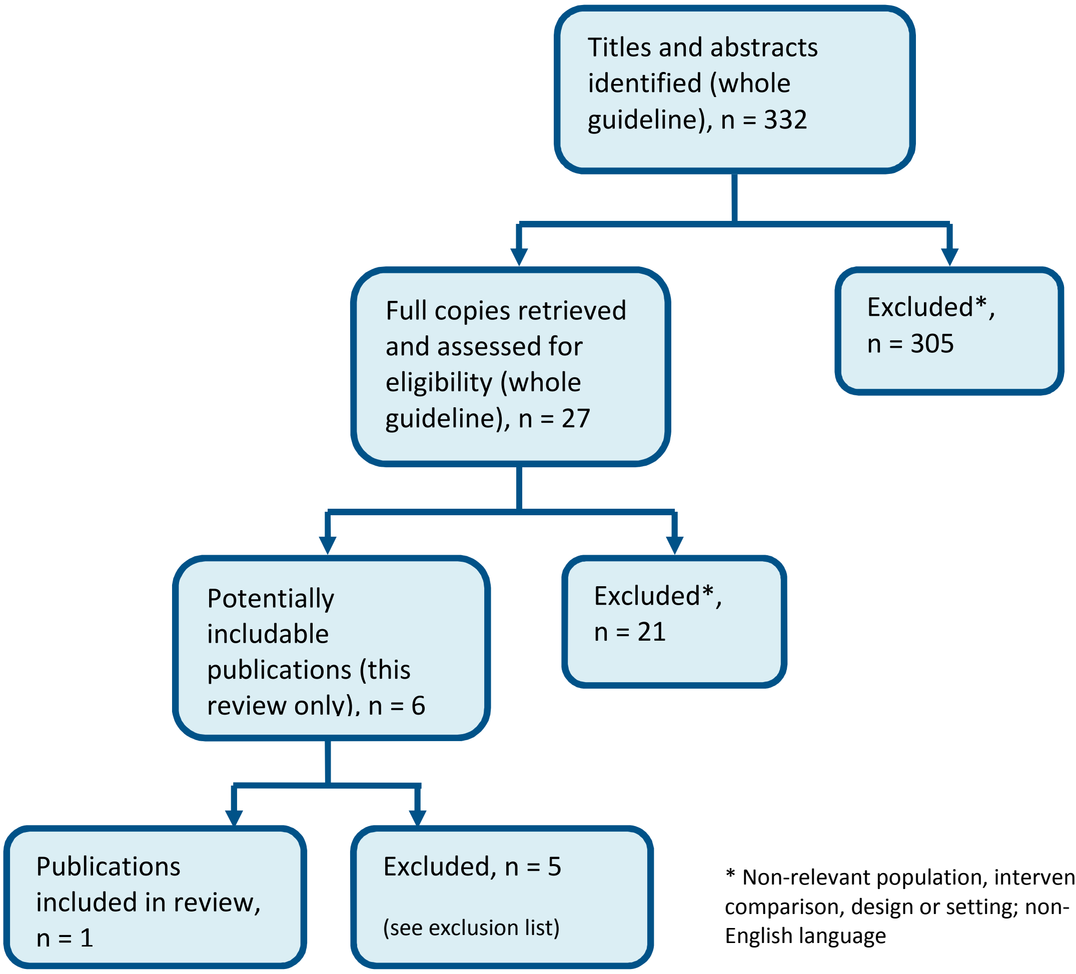
Figure 19: Economic article selection: compression vs. interventional treatment



E.5 Chapter 9 – interventional treatment

E.5.1 Stripping surgery vs. foam sclerotherapy

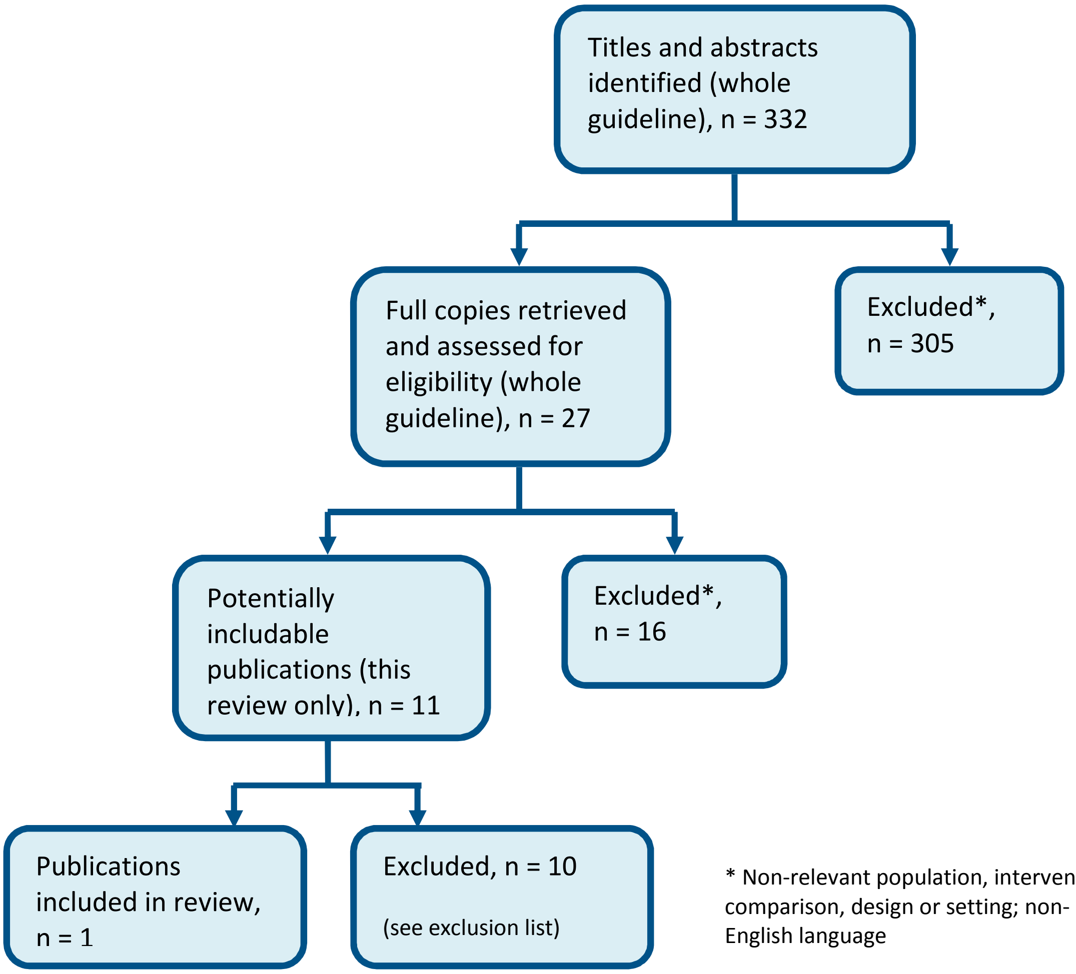
Figure 20: Economic article selection: stripping surgery vs. foam sclerotherapy



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.5.2 Stripping surgery vs. endothermal ablation

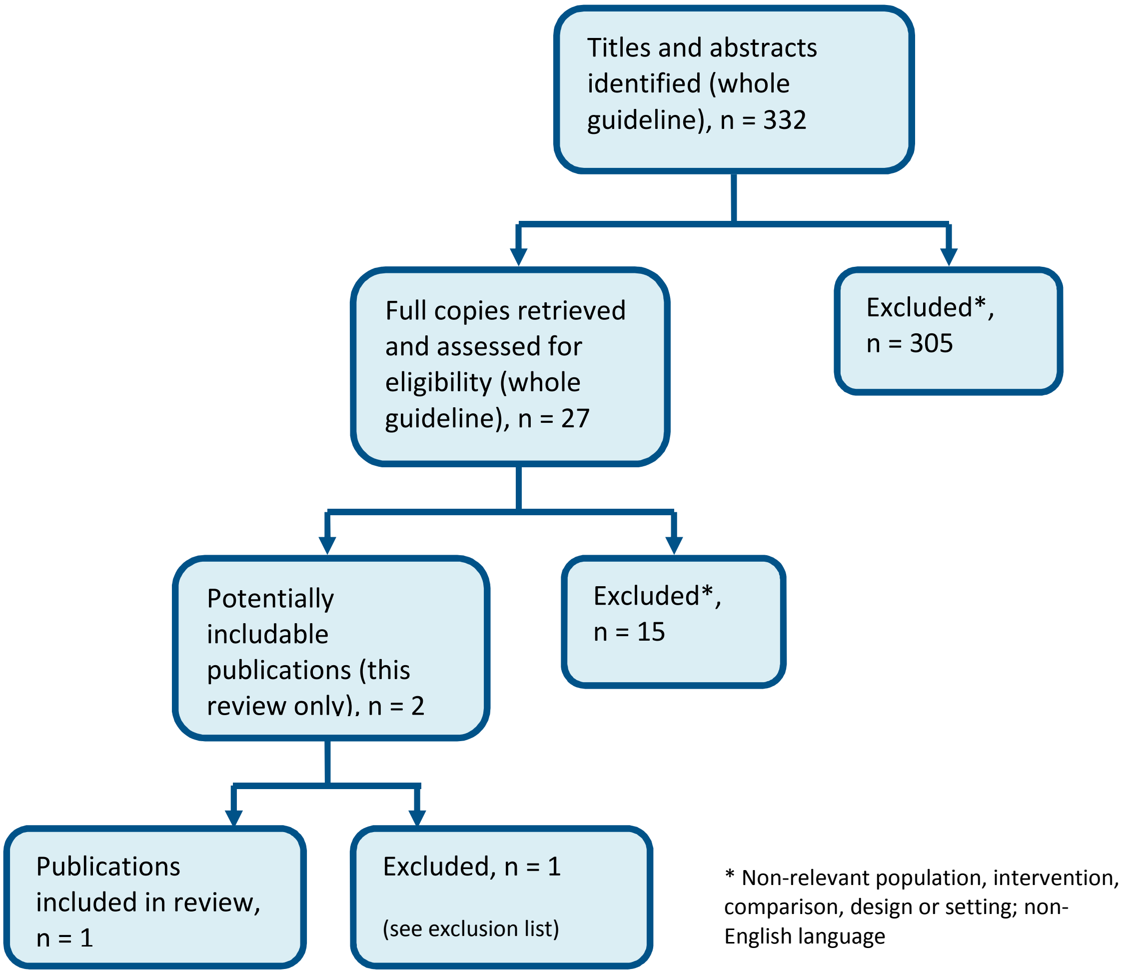
Figure 21: Economic article selection: stripping surgery vs. endothermal ablation



* Non-relevant population, intervention, comparison, design or setting; non-English language

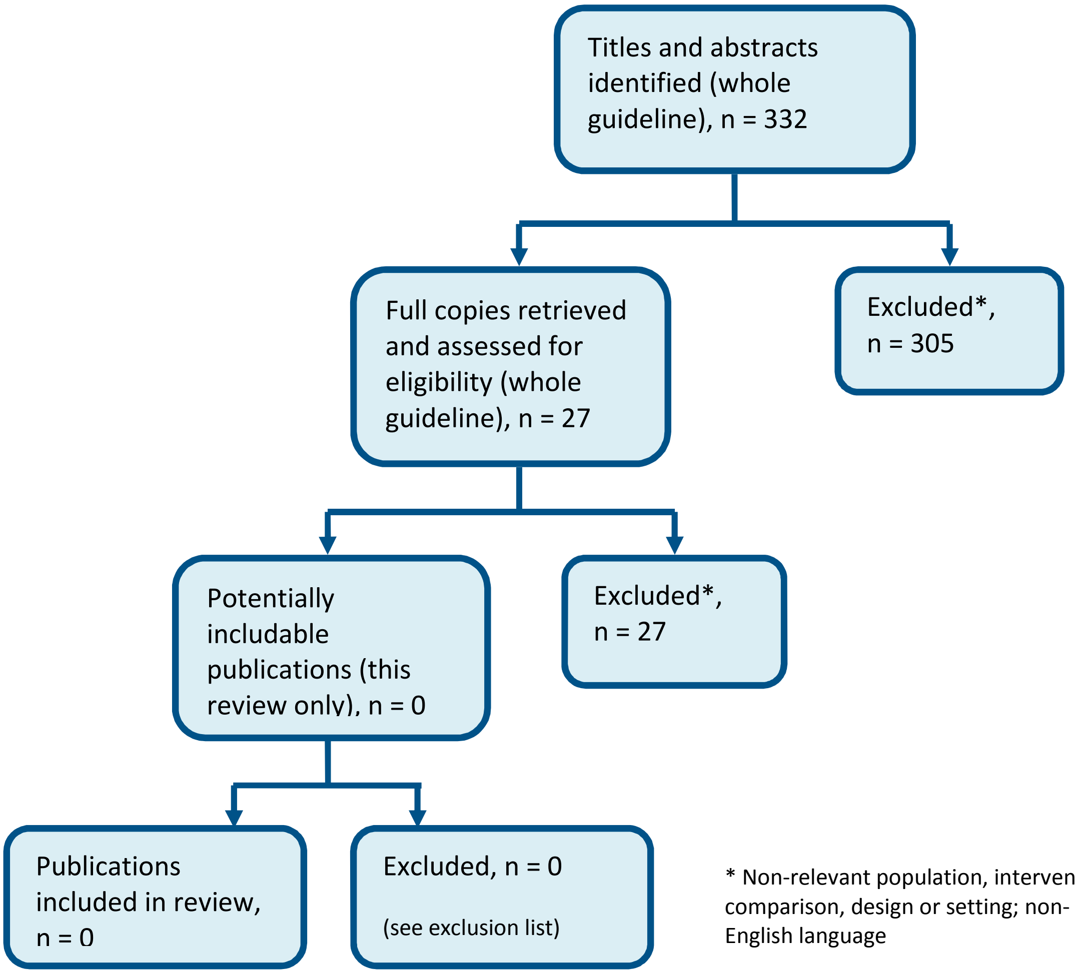
E.5.3 Foam sclerotherapy vs. endothermal ablation

Figure 22: Economic article selection: foam sclerotherapy vs. endothermal ablation



E.5.4 Tributary treatment: avulsion vs. foam sclerotherapy

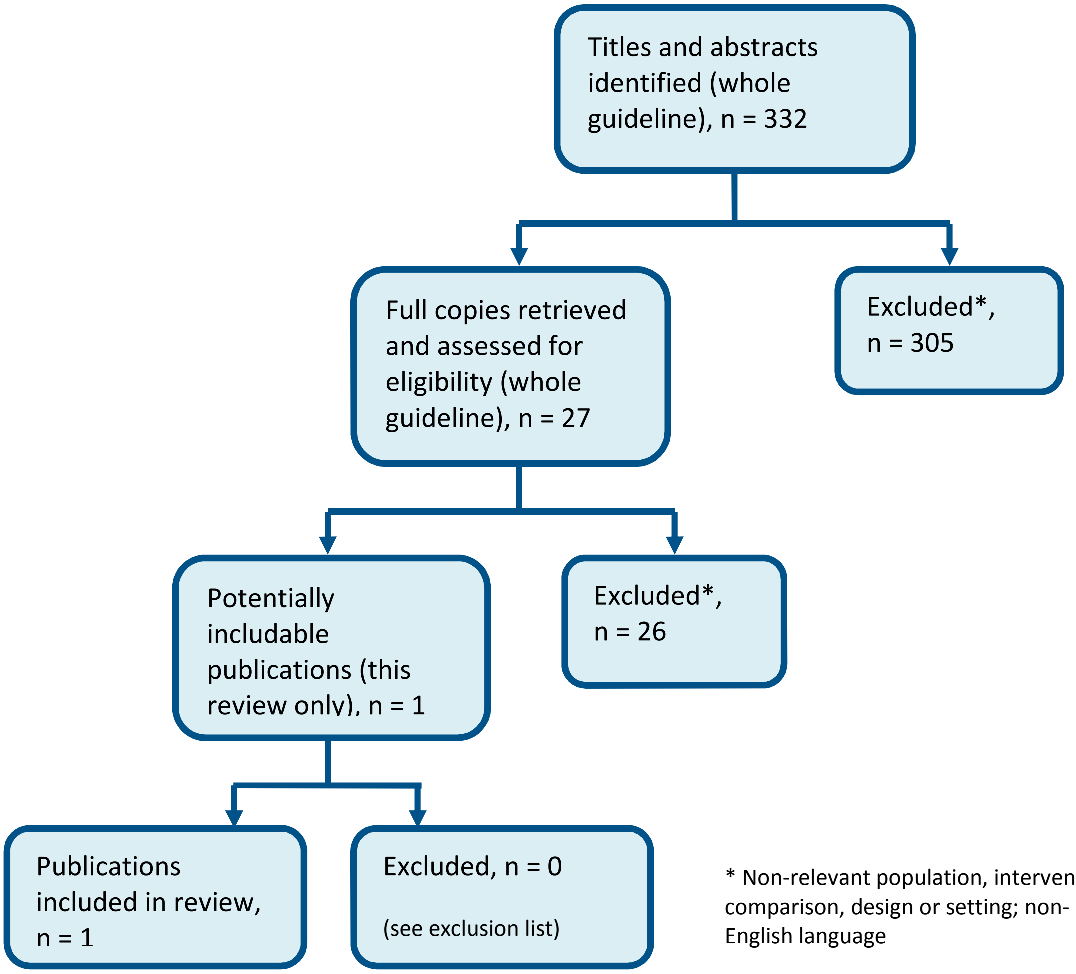
Figure 23: Economic article selection: avulsion vs. foam sclerotherapy



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.5.5 Truncal treatment and tributary treatment vs. truncal treatment alone

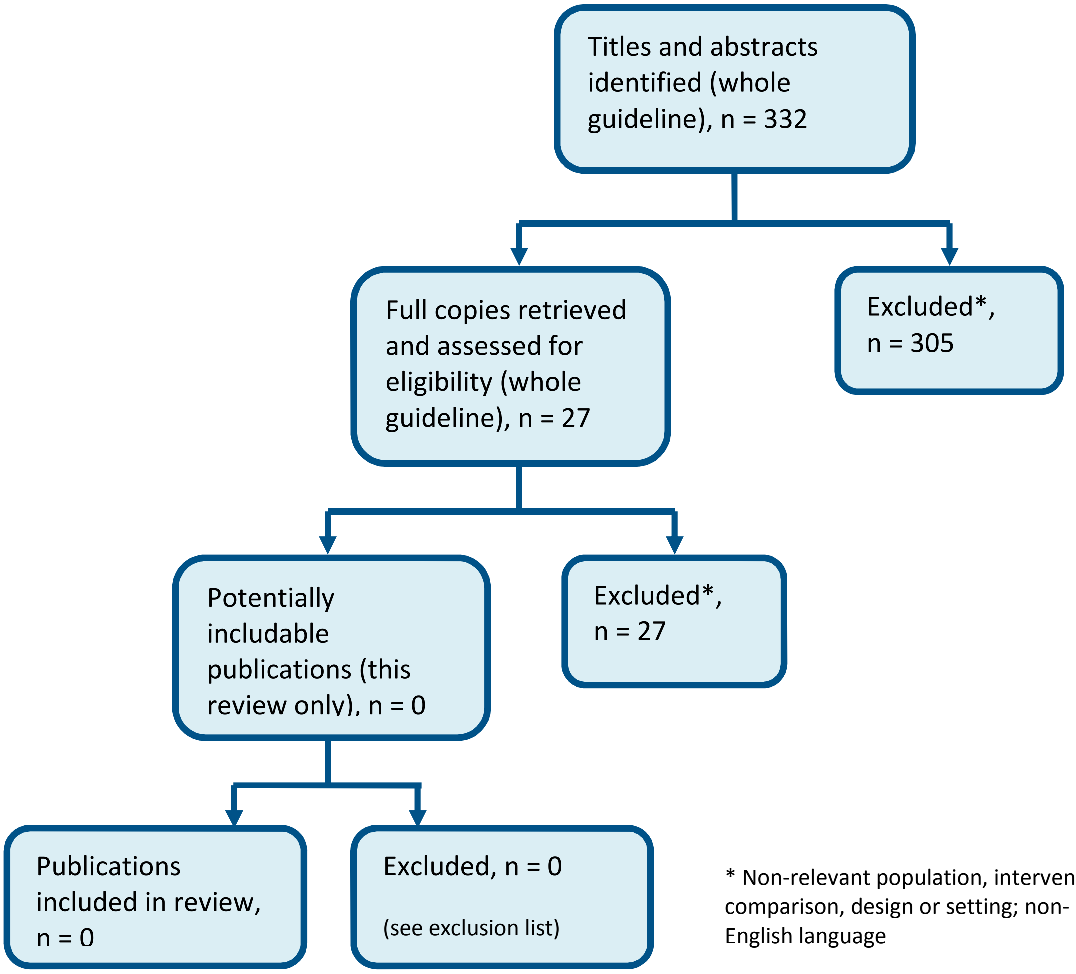
Figure 24: Economic article selection: truncal treatment and tributary treatment vs. truncal treatment alone



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.6 Chapter 10 – compression after treatment

Figure 25: Economic article selection: compression after treatment



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix F: Literature search strategies

Contents

Introduction

Search strategies used for the **Varicose Veins guideline** were run in accordance with the Guidelines Manual (NICE, 2009). All searches were run finally on **17 October 2012** unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

Clinical searches

Searches for **clinical reviews** were run in Medline (OVID), Embase (OVID), and the Cochrane Library (Wiley). Typically, searches were constructed in the following way:

- A PICO format was used for intervention searches. **Population** (P) terms were combined with **Intervention** (I) and sometimes **Comparison** (C) terms (as indicated in the tables under each individual question in Section F.3). An intervention can be a drug, a procedure or a diagnostic test. **Outcome** (O) terms are rarely used in search strategies for interventions. Study type filters (F.1) were added where appropriate.

In addition to the databases outlined above, searches F.3.1 and F.3.4 were run in Cinahl (EBSCO), and F.3.1 in PsycINFO (OVID).

Economic searches

Searches for **economic evidence** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Cochrane (Wiley) interface. For Medline and Embase an economic filter (see F.1.4) was applied to the standard population. All other searches were conducted using only population terms.

F.1 Study design search terms

F.1.1 Systematic review (SR) search terms

Medline search terms

1.	Meta-analysis/
2.	Meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	or/1-9

Embase search terms

1.	Systematic review/
2.	Meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10.	cochrane.jw.
11.	or/1-10

F.1.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1.	Randomized controlled trial.pt.
2.	Controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.

6.	Clinical trials as topic.sh.
7.	trial*.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	Crossover procedure/
7.	Single blind procedure/
8.	Randomized controlled trial/
9.	Rouble blind procedure/
10.	or/1-9

F.1.3 Observational studies search terms

Medline search terms

1.	Epidemiologic studies/
2.	exp Case control studies/
3.	exp Cohort studies/
4.	Cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow-up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	Clinical study/
2.	exp Case control study/
3.	Family study/
4.	Longitudinal study/
5.	Retrospective study/
6.	Prospective study/
7.	Cross-sectional study/
8.	Cohort analysis/
9.	Follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow-up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.

15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

F.1.4 Health economic search terms

Medline search terms

1.	Economics/
2.	Value of life/
3.	exp "Costs and cost analysis"/
4.	exp Economics, Hospital/
5.	exp Economics, Medical/
6.	exp Resource allocation/
7.	Economics, Nursing/
8.	Economics, Pharmaceutical/
9.	exp "Fees and charges"/
10.	exp Budgets/
11.	budget*.ti,ab.
12.	cost*.ti,ab.
13.	(economic* or pharmaco?economic*).ti,ab.
14.	(price* or pricing*).ti,ab.
15.	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	resourc* allocat*.ti,ab.
18.	(fund or funds or funding* or funded).ti,ab.
19.	(ration or rations or rationing* or rationed).ti,ab.
20.	ec.fs.
21.	or/1-20

Embase search terms

1.	Health economics/
2.	exp Economic evaluation/
3.	exp Health care cost/
4.	exp Fee/
5.	Budget/
6.	Funding/
7.	Resource allocation/
8.	budget*.ti,ab.
9.	cost*.ti,ab.
10.	(economic* or pharmaco?economic*).ti,ab.
11.	(price* or pricing*).ti,ab.
12.	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	resourc* allocat*.ti,ab.
15.	(fund or funds or funding* or funded).ti,ab.
16.	(ration or rations or rationing* or rationed).ti,ab.

F.1.5 Quality of life search terms

Medline search terms

1.	Quality-adjusted life years/
2.	Sickness impact profile/
3.	(quality adj2 (wellbeing or well being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	Quality adjusted life year/
2.	"Quality of life index"/
3.	Short form 12/ or Short form 20/ or Short form 36/ or Short form 8/
4.	Sickness impact profile/
5.	(quality adj2 (wellbeing or well being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.

22.	or/1-21

F.1.6 Diagnostic accuracy

Medline search terms

1.	exp "Sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(prognos* or predict*).ti,ab,hw.
5.	(PPV or NPV).ti,ab.
6.	Likelihood function/
7.	(ROC curve* or AUC).ti,ab.
8.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	(improve* adj3 (outcome* or result*)).ti,ab.
11.	Treatment outcome/
12.	or/1-11

Embase search terms

1.	exp "Sensitivity and specificity"/
2.	Diagnostic accuracy/
3.	Diagnostic test accuracy study/
4.	Treatment outcome/
5.	(prognos* or predict*).ti,ab,hw.
6.	(sensitivity or specificity).ti,ab.
7.	((pre test or pretest or post test) adj probability).ti,ab.
8.	(PPV or NPV).ti,ab.
9.	likelihood ratio*.ti,ab.
10.	(ROC curve* or AUC).ti,ab.
11.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
12.	(improve* adj3 (outcome* or result*)).ti,ab.
13.	gold standard.ab.
14.	or/1-13

F.2 Standard population search strategy

Medline search terms

1.	exp Varicose veins/
2.	(varicos* adj5 vein*).ti,ab.
3.	Saphenous vein/
4.	(sapheno* adj3 (vein* or junction* or incompet* or reflux or insufficien*)).ti,ab.
5.	exp Coronary artery bypass/
6.	((coronary or bypass) and graft).ti,ab.
7.	(3 or 4) not (5 or 6)
8.	1 or 2 or 7

9.	Venous insufficiency/
10.	((venous or vein* or varico* or truncal or valvular) adj3 (insufficien* or incompet* or disorder* or reflux)).ti,ab.
11.	((venous or varico*) adj disease*).ti,ab.
12.	((perforator or superficial or tortuous) adj3 vein*).ti,ab.
13.	(varix or varices or varicosi* or ceap).ti,ab.
14.	((varico* or venous or vein*) adj3 ulcer*).ti,ab.
15.	or/9-14
16.	exp Lower extremity/
17.	(lower adj2 extremit*).ti,ab.
18.	(leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or pelvis or pelvic or vulva* or vulvo* or ovari* or ovary or vagina* or uterus or uterin*).ti,ab.
19.	or/16-18
20.	8 or (15 and 19)
21.	limit 20 to english language
22.	Letter/
23.	Editorial/
24.	News/
25.	exp Historical article/
26.	Anecdotes as topic/
27.	Comment/
28.	Case report/
29.	(letter or comment*).ti.
30.	or/22-29
31.	30 not (Randomized controlled trial/ or random*.ti,ab.)
32.	Animals/ not Humans/
33.	exp Animals, Laboratory/
34.	exp Animal experimentation/
35.	exp Models, Animal/
36.	exp Rodentia/
37.	(rat or rats or mouse or mice).ti.
38.	or/31-37
39.	21 not 38

Embase search terms

1.	Varicosis/
2.	Leg varicosis/
3.	(varicos* adj5 vein*).ti,ab.
4.	Saphenous vein/
5.	(sapheno* adj3 (vein* or junction or incompet* or reflux or insufficien*)).ti,ab.
6.	exp Coronary artery bypass graft/
7.	((coronary or bypass) and graft).ti,ab.
8.	(4 or 5) not (6 or 7)
9.	1 or 2 or 3 or 8
10.	exp Vein insufficiency/
11.	((venous or vein* or varico* or truncal or valvular) adj3 (insufficien* or incompet* or disorder*

	or reflux)).ti,ab.
12.	((venous or varico*) adj disease*).ti,ab.
13.	((perforator or superficial or tortuous) adj3 vein*).ti,ab.
14.	(varix or varices or varicosi* or ceap).ti,ab.
15.	((varico* or venous or vein*) adj3 ulcer*).ti,ab.
16.	or/10-15
17.	exp Leg/
18.	(lower adj2 extremit*).ti,ab.
19.	(leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or pelvis or pelvic or vulva* or vulvo* or ovari* or ovary or vagina* or uterus or uterin*).ti,ab.
20.	or/17-19
21.	9 or (16 and 20)
22.	limit 21 to english language
23.	Letter.pt. or Letter/
24.	Note.pt.
25.	Editorial.pt.
26.	Case report/ or Case study/
27.	(letter or comment*).ti.
28.	or/23-27
29.	28 not (randomized controlled trial/ or random*.ti,ab.)
30.	Animal/ not Human/
31.	Nonhuman/
32.	exp Animal experiment/
33.	exp Experimental animal/
34.	Animal model/
35.	exp Rodent/
36.	(rat or rats or mouse or mice).ti.
37.	or/29-36
38.	22 not 37

1 **Cinahl search terms**

S1	(MH "Varicose Veins")
S2	varicos* n5 vein*
S3	(MH "Saphenous Vein")
S4	sapheno* and (vein* or junction* or incompet* or reflux or insufficien*)
S5	(MH "Coronary Artery Bypass+")
S6	(S3 or S4) not S5
S7	S1 or S2 or S6
S8	(MH "Venous Insufficiency")
S9	(venous or vein* or varico* or truncal or valvular) and (insufficien* or incompet* or disorder* or reflux)
S10	(perforator n3 vein*) or (superficial n3 vein*) or (tortuous n3 vein*)
S11	varix or varices or varicosi* or ceap
S12	(venous n1 disease*) or (varico* n1 disease*)
S13	(varico* n3 ulcer*) or (vein* n3 ulcer*) or (venous n3 ulcer*)
S14	S8 or S9 or S10 or S11 or S12 or S13

S15	(MH "Lower Extremity+")
S16	lower n2 extremit*
S17	leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or pelvis or pelvic or vulva* or vulvo* or ovari* or ovary or vagina* or uterus or uterin*
S18	S15 or S16 or S17
S19	S7 or (S14 and S18)

Cochrane search terms

#1	MeSH descriptor Varicose Veins explode all trees
#2	(varicos* NEAR/5 vein*):ti,ab
#3	MeSH descriptor Saphenous Vein, this term only
#4	(sapheno* NEAR/3 (vein* or junction* or incompet* or reflux or insufficien*)):ti,ab
#5	MeSH descriptor Coronary Artery Bypass explode all trees
#6	((coronary or bypass) and graft):ti,ab
#7	((#3 or #4) and not (#5 OR #6))
#8	(#1 or #2 or #7)
#9	MeSH descriptor Venous Insufficiency, this term only
#10	((venous or vein* or varico* or truncal or valvular) NEAR/3 (insufficien* or incompet* or disorder* or reflux)):ti,ab
#11	((perforator or superficial or tortuous) NEAR/3 vein*):ti,ab
#12	(varix or varices or varicosi* or ceap):ti,ab
#13	((varico* or vein* or venous) NEAR/3 ulcer*):ti,ab
#14	((venous or varico*) NEXT disease*):ti,ab
#15	(#9 or #10 or #11 or #12 or #13 or #14)
#16	MeSH descriptor Lower Extremity explode all trees
#17	(lower NEAR/2 extremit*):ti,ab
#18	(leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or pelvis or pelvic or vulva* or vulvo* or ovari* or ovary or vagina* or uterus or uterin*):ti,ab
#19	(#16 or #17 or #18)
#20	(#8 or (#15 and #19))

F.3 Searches by specific questions

F.3.1 Patient information

Q. What are the perceptions and expectations of people with varicose veins (e.g. natural history, treatment) and how can they be addressed?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Patient information	None	All years - 17/10/2012

Medline search terms

1.	((client* or patient* or user* or carer* or consumer* or customer* or health) adj3 (information* or educat* or knowledge or literacy or belief* or perception* or understanding or expectation* or prefer* or satisfaction or acceptance or compliance or adherence or concordance)).ti,ab,hw.
2.	(information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab,hw.

3.	((patient* or user* or carer* or consumer* or customer* or health) adj3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)).ti,ab.
4.	Telemedicine/
5.	Interview/
6.	Telephone/
7.	Publications/
8.	Pamphlets/
9.	Internet/
10.	or/1-9

Embase search terms

1.	((client* or patient* or user* or carer* or consumer* or customer* or health or medical) adj3 (information* or educat* or knowledge or literacy or belief* or perception* or understanding or expectation* or attitude* or prefer* or satisfaction or acceptance or compliance or adherence or concordance or advocacy)).ti,ab,hw.
2.	(information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab,hw.
3.	((patient* or user* or carer* or consumer* or customer* or health) adj3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)).ti,ab.
4.	exp Telehealth/
5.	exp Interview/
6.	Telephone/
7.	Publication/
8.	Internet/
9.	or/1-8

Cinahl search terms

S1.	(MH "Varicose Veins")
S2.	varicos* n5 vein*
S3.	(MH "Saphenous Vein")
S4.	sapheno* and (vein* or junction* or incompet* or reflux or insufficien*)
S5.	(MH "Coronary Artery Bypass+")
S6.	(S3 or S4) not S5
S7.	S1 or S2 or S6
S8.	(MH "Venous Insufficiency")
S9.	(venous or vein* or varico* or truncal or valvular) and (insufficien* or incompet* or disorder* or reflux)
S10.	(perforator n3 vein*) or (superficial n3 vein*) or (tortuous n3 vein*)
S11.	varix or varices or varicosi* or ceap
S12.	(venous n1 disease*) or (varico* n1 disease*)
S13.	(varico* n3 ulcer*) or (vein* n3 ulcer*) or (venous n3 ulcer*)
S14.	S8 or S9 or S10 or S11 or S12 or S13
S15.	(MH "Lower Extremity+")
S16.	lower n2 extremit*
S17.	leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or pelvis or pelvic or vulva* or vulvo* or ovari* or ovary or vagina* or uterus or uterin*

S18.	S15 or S16 or S17
S19.	S7 or (S14 and S18)
S20.	information* n2 need* or information* n2 requirement* or information* n2 support* or information* n2 seek* or information* n2 access* or information* n2 disseminat*
S21.	patient* n3 information* or patient* n3 knowledge or patient* n3 educat*
S22.	carer* n3 information* or carer* n3 knowledge or carer* n3 educat* or health* n3 information* or health* n3 educat*
S23.	patient* n3 literature or patient* n3 leaflet* or patient* n3 booklet* or patient* n3 pamphlet* or patient* n3 questionnaire* or patient* n3 survey* or patient* n3 handout* or patient* n3 internet or patient* n3 website*
S24.	TI (patient* or satisfaction*) and (questionnaire* or survey*)
S25.	(MH "Access to Information+")
S26.	S20 or S21 or S22 or S23 or S24 or S25
S27.	S19 and S26
S28.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S29.	S27 not S28
S30.	English Language OR Exclude Medline records
S31.	S29 and S30

1 **Cochrane search terms**

#1.	MeSH descriptor Patient Acceptance of Health Care, this term only
#2.	MeSH descriptor Patient Compliance, this term only
#3.	MeSH descriptor Patient Education as Topic, this term only
#4.	MeSH descriptor Patient Preference, this term only
#5.	MeSH descriptor Patient Satisfaction, this term only
#6.	MeSH descriptor Consumer Health Information, this term only
#7.	MeSH descriptor Consumer Satisfaction, this term only
#8.	MeSH descriptor Health Literacy, this term only
#9.	MeSH descriptor Health Knowledge, Attitudes, Practice, this term only
#10.	MeSH descriptor Telemedicine, this term only
#11.	MeSH descriptor Access to Information, this term only
#12.	MeSH descriptor Information Dissemination, this term only
#13.	MeSH descriptor Information Seeking Behavior, this term only
#14.	MeSH descriptor Pamphlets, this term only
#15.	MeSH descriptor Internet, this term only
#16.	MeSH descriptor Interviews as Topic explode all trees
#17.	MeSH descriptor Telephone, this term only
#18.	MeSH descriptor Telemedicine, this term only
#19.	((client* or patient* or user* or carer* or consumer* or customer* or health) NEAR/3 (information* or educat* or knowledge or literacy or belief* or perception* or attitude* or understanding or expectation* or prefer* or satisfaction or acceptance or compliance or adherence or concordance)):ti,ab
#20.	(information* NEAR/3 (need* or requirement* or support* or seek* or access* or

	disseminat*)):ti,ab
#21.	((patient* or user* or carer* or consumer* or customer* or health) NEAR/3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)):ti,ab
#22.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)

PsycINFO search terms

1.	(varicos* adj5 vein*).ti,ab.
2.	((venous or vein* or varico* or truncal or valvular) adj3 (insufficien* or incompet* or disorder* or reflux)).ti,ab.
3.	((venous or varico*) adj disease*).ti,ab.
4.	((perforator or superficial or tortuous) adj3 vein*).ti,ab.
5.	(varix or varices or varicosi* or ceap).ti,ab.
6.	((varico* or venous or vein*) adj3 ulcer*).ti,ab.
7.	(leg* or limb* or calf or calves or thigh* or groin* or ankle* or foot or feet or lower extremit*).ti,ab.
8.	(2 or 3 or 4 or 5 or 6) and 7
9.	1 or 8

F.3.2 Assessment for referral

F.3.2.1 Disease progression

Q. **a) In people with leg varicose veins at CEAP class C2 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C3, ii) C4* iii) C6?**

b) In people with leg varicose veins at CEAP class C3 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C4* ii) C6?

c) In people with leg varicose veins at CEAP class C4* which signs, symptoms and/or patient characteristics are associated with disease progression to C6?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Disease classification AND disease progression	Observational studies* [Medline and Embase only]	All years - 17/10/2012

*Observational search filter in F.1.3 expanded for this question

Medline search terms

1.	(CEAP or C2 or C3 or C4 or C5 or C6 or C-2 or C-3 or C-4 or C-5 or C-6).ti,ab.
2.	(class* or stage* or staging).ti,ab.
3.	(skin adj2 (discol* or change* or pigment*)).ti,ab.
4.	(ulcer* or oedem* or edem* or lipoderm* or eczema or atroph*).ti,ab.
5.	or/1-4
6.	Disease progression/
7.	Natural history/
8.	Risk factors/
9.	(risk* or course* or predict* or incidence or prognos* or progress* or natural history).ti,ab.

10.	or/6-9
11.	5 and 10
12.	Epidemiologic studies/
13.	exp Case control studies/
14.	exp Cohort studies/
15.	Cross-sectional studies/
16.	case control.ti,ab.
17.	((follow-up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
18.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
19.	(cohort* or group* or subgroup* or participant*).ti,ab.
20.	or/12-19
21.	11 and 20

Embase search terms

1.	Disease classification/
2.	(CEAP or C2 or C3 or C4 or C5 or C6 or C-2 or C-3 or C-4 or C-5 or C-6).ti,ab.
3.	(class* or stage* or staging).ti,ab.
4.	(skin adj2 (discol* or change* or pigment*)).ti,ab.
5.	(ulcer* or oedem* or edem* or lipoderm* or eczema or atroph*).ti,ab.
6.	or/1-5
7.	Risk factor/
8.	Disease course/
9.	Disease exacerbation/
10.	Predictive value/
11.	(risk* or course* or predict* or incidence or prognos* or progress* or natural history).ti,ab.
12.	or/7-11
13.	6 and 12
14.	Clinical study/
15.	exp Case control study/
16.	Family study/
17.	Longitudinal study/
18.	Retrospective study/
19.	Prospective study/
20.	Cross-sectional study/
21.	Cohort analysis/
22.	Follow-up/
23.	case control.ti,ab.
24.	((follow-up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
25.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
26.	(cohort* or group* or subgroup* or participant*).ti,ab.
27.	or/14-26
28.	13 and 27

F.3.2.2 Prediction of treatment outcomes

Q. In people with leg varicose veins are there any factors (clinical signs and symptoms or patient reported outcomes) that would predict increased benefits or harms from interventional treatments for varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Interventional treatments AND risk factors	RCTs, SRs and Observational studies* [Medline and Embase only]	All years - 17/10/2012

*Observational search filter in F.1.3 expanded for this question

Medline search terms

1.	Vascular surgical procedures/
2.	Ablation techniques/
3.	Laser therapy/
4.	Sclerotherapy/
5.	Sclerosing solutions/
6.	Sodium tetradecyl sulfate/
7.	(scleros* or sclerotherap* or sclero therap* or UGFS).ti,ab.
8.	(polidocanol or POL or sodium tetradecyl or STS or sotradecol or fibrovein or sclerovein).ti,ab.
9.	(foam or microfoam or liquid).ti,ab.
10.	(strip* or cryostrip* or saphenect* or disconnect*).ti,ab.
11.	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or trans illuminate* or transilluminate* or trivex).ti,ab.
12.	surg*.ti.
13.	(ablat* or endoluminal or laser or radiofrequency or radio frequency or endovenous or RFA or EVLT).ti,ab.
14.	or/1-13
15.	Risk factors/
16.	Risk assessment/
17.	exp Treatment outcome/
18.	Prognosis/
19.	Disease progression/
20.	(risk* or benefit* or harm* or predisp* or pre dispos* or prognos* or course* or progress* or predict* or characteristic* or factor*).ti,ab.
21.	(age or gender or sex or BMI or heredity or weight or body mass or family history or obes* or pregnan* or birth or childbirth or lifestyle or occupation or contracept* or mobility or smoking or drinking or co-morb* or comorb* or reflux).ti,ab.
22.	or/15-21
23.	14 and 22

Embase search terms

1.	Phlebectomy/
2.	Sclerotherapy/
3.	Sclerosing agent/
4.	Tetradecyl sulfate sodium/
5.	Polidocanol/

6.	Vein stripping/
7.	Laser surgery/
8.	Radiofrequency ablation/
9.	Endovenous laser ablation/
10.	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or trans illuminate* or transilluminate* or trivex).ti,ab.
11.	(scleros* or sclerotherap* or UGFS).ti,ab.
12.	(polidocanol or POL or sodium tetradecyl or STS or sotradecol or fibrovein or sclerovein).ti,ab.
13.	(foam or microfoam or liquid).ti,ab.
14.	(strip* or cryostrip* or saphenect* or disconnect*).ti,ab.
15.	(ablat* or endoluminal or laser or radiofrequency or radio frequency or endovenous or RFA or EVLT).ti,ab.
16.	surg*.ti.
17.	or/1-16
18.	risk.hw.
19.	predict*.hw.
20.	Treatment outcome/
21.	Treatment failure/
22.	Treatment response/
23.	Prognosis/
24.	Disease course/
25.	(risk* or benefit* or harm* or predisp* or pre dispos* or prognos* or course* or progress* or predict* or characteristic* or factor*).ti,ab.
26.	(age or gender or sex or BMI or heredity or weight or body mass or family history or obes* or pregnan* or birth or childbirth or lifestyle or occupation or contracept* or mobility or smoking or drinking or co-morb* or comorb* or reflux).ti,ab.
27.	or/18-26
28.	17 and 27

1 **Cochrane search terms**

#1.	MeSH descriptor Vascular Surgical Procedures, this term only
#2.	MeSH descriptor Ablation Techniques, this term only
#3.	MeSH descriptor Laser Therapy, this term only
#4.	MeSH descriptor Sclerotherapy, this term only
#5.	MeSH descriptor Sclerosing Solutions, this term only
#6.	MeSH descriptor Sodium Tetradecyl Sulfate, this term only
#7.	(scleros* or sclerotherap* or "sclero therapy" or UGFS):ti,ab
#8.	(polidocanol or POL or "sodium tetradecyl" or STS or sotradecol or fibrovein or sclerovein):ti,ab
#9.	(foam or microfoam or liquid):ti,ab
#10.	(strip* or cryostrip* or saphenect* or disconnect*):ti,ab
#11.	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or "trans illuminated" or transilluminate* or trivex):ti,ab
#12.	(ablat* or endoluminal or laser or radiofrequency or "radio frequency" or endovenous or RFA or EVLT):ti,ab
#13.	surg*:ti
#14.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)

#15.	MeSH descriptor Risk Factors, this term only
#16.	MeSH descriptor Risk Assessment, this term only
#17.	MeSH descriptor Treatment Outcome explode all trees
#18.	MeSH descriptor Prognosis, this term only
#19.	MeSH descriptor Disease Progression, this term only
#20.	(risk* or benefit* or harm* or predisp* or "pre disposed" or "pre disposition" or prognos* or course* or progress* or predict* or characteristic* or factor*):ti,ab
#21.	(age or gender or sex or BMI or heredity or weight or "body mass" or "family history" or obes* or pregnan* or birth or childbirth or lifestyle or occupation or contracept* or mobility or smoking or drinking or co-morbidity or comorbidities or comorb* or reflux):ti,ab
#22.	(#15 or #16 or #17 or #18 or #19 or #20 or #21)
#23.	(#14 and #22)

F.3.3 Assessment for treatment

The following two questions were searched using a single strategy:

Q1. Does the use of duplex ultrasound during assessment improve outcome after interventional treatment compared to no duplex scanning in people with leg varicose veins?

Q2. What is the diagnostic accuracy of hand held Doppler (HHD) compared to gold standard of duplex scanning when used in patients with varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Duplex ultrasound	Diagnostic accuracy [Medline and Embase only]	All years – 17/10/2012

Medline search terms

1.	exp Ultrasonography, Doppler/
2.	Ultrasonography, Interventional/
3.	(ultraso* or echograph* or sonogra* or Doppler or duplex or DU or DUS).ti,ab.
4.	or/1-3

Embase search terms

1.	Echography/
2.	Doppler echography/
3.	Endoscopic echography/
4.	Color ultrasound flowmetry/
5.	Diagnostic imaging/
6.	(ultraso* or echograph* or sonogra* or Doppler or duplex or DU or DUS).ti,ab.
7.	or/1-6

Cochrane search terms

#1.	MeSH descriptor Ultrasonography, Doppler explode all trees
#2.	MeSH descriptor Ultrasonography, Interventional, this term only
#3.	(ultraso* or echograph* or sonogra* or Doppler or duplex or DU or DUS):ti,ab
#4.	(#1 or #2 or #3)
#5.	MeSH descriptor Sensitivity and specificity explode all trees

#6.	MeSH descriptor Prognosis, this term only
#7.	MeSH descriptor Treatment outcome, this term only
#8.	MeSH descriptor Likelihood functions, this term only
#9.	(sensitivity or specificity):ti,ab
#10.	(("pre test" or pretest or "post test") NEXT probability):ti,ab
#11.	(prognos* or predict*):ti,ab
#12.	(PPV or NPV):ti,ab
#13.	("ROC curve*" or AUC):ti,ab
#14.	(diagnos* NEAR/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)):ti,ab
#15.	"gold standard":ab
#16.	(improve* NEAR/3 (outcome* or result*)):ti,ab
#17.	(#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
#18.	(#4 and #17)

F.3.4 Conservative management

The following four questions were searched using a single strategy:

Q1. What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins?

Q2. What is the clinical and cost effectiveness and safety of compression therapy compared with foam sclerotherapy in people with leg varicose veins?

Q3. What is the clinical and cost effectiveness and safety of compression therapy compared with stripping surgery in people with leg varicose veins?

Q4. What is the clinical and cost effectiveness and safety of compression therapy compared with endothermal ablation in people with leg varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Compression therapy	RCTs, SRs and Observational studies [Medline and Embase only]	All years - 17/10/2012

Medline search terms

1.	Pressure/
2.	Bandages/
3.	exp Compression bandages/
4.	Intermittent pneumatic compression devices/
5.	((compressi* or pressure) and (hosiery or stocking* or bandag*)).ti,ab.
6.	((compressi* or pressure or hosiery or stocking* or bandag*) adj2 (therap* or treatment* or device* or eccentric or pneumatic)).ti,ab.
7.	((elastic or system* or support) adj2 (hosiery or stocking* or bandag*)).ti,ab.
8.	(external* adj2 compression).ti,ab.
9.	conservative treatment*.ti,ab.
10.	or/1-9

Embase search terms

1.	Compression/

2.	exp Compression therapy/
3.	Compression bandage/
4.	*Bandage/
5.	Compression garment/
6.	Intermittent pneumatic compression device/
7.	((compressi* or pressure) and (hosiery or stocking* or bandag*)).ti,ab.
8.	((compressi* or pressure or hosiery or stocking* or bandag*) adj2 (therap* or treatment* or device* or eccentric or pneumatic)).ti,ab.
9.	((elastic or system* or support) adj2 (hosiery or stocking* or bandag*)).ti,ab.
10.	(external* adj2 compression).ti,ab.
11.	conservative treatment*.ti,ab.
12.	or/1-11

Cinahl search terms

S1	(MH "Compression therapy")
S2	(MH "Compression garments")
S3	(compressi* or pressure) and (hosiery or stocking* or bandag*)
S4	(compressi* n2 therap*) or (compressi* n2 treatment) or (compressi* n2 device*) or (compressi* n2 eccentric) or (compressi* n2 pneumatic) or (pressure n2 therap*) or (pressure n2 treatment)
S5	(elastic n2 hosiery) or (elastic n2 stocking*) or (elastic n2 bandag*) or (system n2 hosiery) or (system n2 stocking*) or (system n2 bandag*) or (support n2 hosiery) or (support n2 stocking*) or (support n2 bandag*)
S6	external* n2 compression
S7	conservative treatment*
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7

Cochrane search terms

#1	MeSH descriptor Pressure, this term only
#2	MeSH descriptor Bandages, this term only
#3	MeSH descriptor Compression Bandages explode all trees
#4	MeSH descriptor Intermittent Pneumatic Compression Devices, this term only
#5	((compressi* or pressure) and (hosiery or stocking* or bandag*)):ti,ab
#6	((compressi* or pressure or hosiery or stocking* or bandag*) NEAR/2 (therap* or treatment* or device* or eccentric or pneumatic)):ti,ab
#7	((elastic or system* or support) NEAR/2 (hosiery or stocking* or bandag*)):ti,ab
#8	(external* NEAR/2 compression):ti,ab
#9	(conservative NEXT treatment*):ti,ab
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)

F.3.5 Interventional treatment

F.3.5.1 Stripping surgery

The following two questions were searched using a single strategy:

Q1. What is the clinical and cost effectiveness and safety of stripping surgery compared with foam sclerotherapy in people with truncal leg varicose veins?

Q2. What is the clinical and cost effectiveness and safety of stripping surgery compared with endothermal ablation in people with truncal leg varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Stripping surgery	RCTs and SRs [Medline and Embase only]	All years - 17/10/2012

Medline search terms

1.	Vascular surgical procedures/
2.	(strip* or cryostrip* or saphenect*).ti,ab.
3.	surg*.ti.
4.	or/1-3

Embase search terms

1.	Vein stripping/
2.	(strip* or cryostrip* or saphenect*).ti,ab.
3.	surg*.ti.
4.	or/1-3

Cochrane search terms

#1	MeSH descriptor Vascular Surgical Procedures, this term only
#2	(strip* or cryostrip* or saphenect*):ti,ab
#3	(#1 or #2)

F.3.5.2 Sclerotherapy

Q. What is the clinical and cost effectiveness of foam sclerotherapy compared with endothermal ablation in people with truncal leg varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Sclerotherapy	RCTs, SRs and Observational studies [Medline and Embase only]	All years – 17/10/2012

Medline search terms

1.	Sclerotherapy/
2.	Sclerosing solutions/
3.	Sodium tetradecyl sulfate/
4.	(scleros* or sclerotherap* or UGFS).ti,ab.
5.	(polidocanol or POL or sodium tetradecyl or STS or sotradecol or fibrovein or sclerovein).ti,ab.
6.	(foam or microfoam or liquid).ti,ab.
7.	or/1-6

Embase search terms

1.	Sclerotherapy/
2.	Sclerosing agent/
3.	Tetradecyl sulfate sodium/
4.	Polidocanol/
5.	(scleros* or sclerotherap* or UGFS).ti,ab.

6.	(polidocanol or POL or sodium tetradecyl or STS or sotradecol or fibrovein or sclerovein).ti,ab.
7.	(foam or microfoam or liquid).ti,ab.
8.	or/1-7

Cochrane search terms

#1	MeSH descriptor Sclerotherapy, this term only
#2	MeSH descriptor Sclerosing solutions, this term only
#3	MeSH descriptor Sodium tetradecyl sulfate, this term only
#4	(scleros* or sclerotherap* or UGFS):ti,ab
#5	(polidocanol or POL or sodium tetradecyl or STS or sotradecol or fibrovein or sclerovein):ti,ab
#6	(foam or microfoam or liquid):ti,ab
#7	(#1 or #2 or #3 or #4 or #5 or #6)

F.3.5.3 Avulsion surgery

The following two questions were searched using a single strategy:

Q1. What is the clinical and cost effectiveness of avulsion surgery compared with sclerotherapy in people with tributary leg varicose veins?

Q2. What is the clinical and cost effectiveness of truncal treatment accompanied by tributary treatment (avulsion or sclerotherapy) compared with truncal treatment alone in people with leg varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filters used	Date parameters
Varicose veins	Avulsion surgery	RCTs, SRs and Observational studies [Medline and Embase only]	All years - 17/10/2012

Medline search terms

1.	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or trans illuminate* or transilluminate* or trivex).ti,ab.
2.	(stab or hook*).ti,ab.
3.	((ambula* or minim* invasive) adj3 surg*).ti,ab.
4.	(branch* adj2 (venous or vein or varicos*)).ti,ab.
5.	tributar*.ti,ab.
6.	or/1-5

Embase search terms

1.	Phlebectomy/
2.	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or trans illuminate* or transilluminate* or trivex).ti,ab.
3.	(stab or hook*).ti,ab.
4.	((ambula* or minim* invasive) adj3 surg*).ti,ab.
5.	(branch* adj2 (venous or vein or varicos*)).ti,ab.
6.	tributar*.ti,ab.
7.	or/1-6

Cochrane search terms

#1	(avuls* or phlebectom* or microphlebectom* or miniphlebectom* or trans illuminate* or transilluminate* or trivex):ti,ab

#2	(stab or hook*):ti,ab
#3	((ambula* or minim* invasive) NEAR/3 surg*):ti,ab
#4	(branch* NEAR/2 (venous or vein or varicos*)):ti,ab
#5	tributar*:ti,ab
#6	(#1 or #2 or #3 or #4 or #5)

F.3.6 Compression post treatment

Q. What is the clinical and cost effectiveness of compression post-ablative treatment compared with ablative treatment alone in people with truncal leg varicose veins?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention	Study filter used	Date parameters
Varicose veins	Compression therapy	RCTs, SRs and Observational studies [Medline and Embase only]	All years - 17/10/2012

Medline search terms

1.	Pressure/
2.	Bandages/
3.	exp Compression bandages/
4.	Intermittent pneumatic compression devices/
5.	((compressi* or pressure) and (hosiery or stocking* or bandag*)).ti,ab.
6.	((compressi* or pressure or hosiery or stocking* or bandag*) adj2 (therap* or treatment* or device* or eccentric or pneumatic)).ti,ab.
7.	((elastic or system* or support) adj2 (hosiery or stocking* or bandag*)).ti,ab.
8.	(external* adj2 compression).ti,ab.
9.	conservative treatment*.ti,ab.
10.	or/1-9

Embase search terms

1.	Compression/
2.	exp Compression therapy/
3.	Compression bandage/
4.	*Bandage/
5.	Compression garment/
6.	Intermittent pneumatic compression device/
7.	((compressi* or pressure) and (hosiery or stocking* or bandag*)).ti,ab.
8.	((compressi* or pressure or hosiery or stocking* or bandag*) adj2 (therap* or treatment* or device* or eccentric or pneumatic)).ti,ab.
9.	((elastic or system* or support) adj2 (hosiery or stocking* or bandag*)).ti,ab.
10.	(external* adj2 compression).ti,ab.
11.	conservative treatment*.ti,ab.
12.	or/1-11

Cinahl search terms

S1	(MH "Compression therapy")
S2	(MH "Compression garments")
S3	(compressi* or pressure) and (hosiery or stocking* or bandag*)
S4	(compressi* n2 therap*) or (compressi* n2 treatment) or (compressi* n2 device*) or

	(compressi* n2 eccentric) or (compressi* n2 pneumatic) or (pressure n2 therap*) or (pressure n2 treatment)
S5	(elastic n2 hosiery) or (elastic n2 stocking*) or (elastic n2 bandag*) or (system n2 hosiery) or (system n2 stocking*) or (system n2 bandag*) or (support n2 hosiery) or (support n2 stocking*) or (support n2 bandag*)
S6	external* n2 compression
S7	conservative treatment*
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7

Cochrane search terms

#1	MeSH descriptor Pressure, this term only
#2	MeSH descriptor Bandages, this term only
#3	MeSH descriptor Compression Bandages explode all trees
#4	MeSH descriptor Intermittent Pneumatic Compression Devices, this term only
#5	((compressi* or pressure) and (hosiery or stocking* or bandag*)):ti,ab
#6	((compressi* or pressure or hosiery or stocking* or bandag*) NEAR/2 (therap* or treatment* or device* or eccentric or pneumatic)):ti,ab
#7	((elastic or system* or support) NEAR/2 (hosiery or stocking* or bandag*)):ti,ab
#8	(external* NEAR/2 compression):ti,ab
#9	(conservative NEXT treatment*):ti,ab
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)

F.4 Economic searches

F.4.1 Economic reviews

Economic searches were run in Medline and Embase by combining the standard population with an economic filter, and limiting by date range (see table below). Economic searches were executed in the HEED and Cochrane (NHS EED and HTA) databases by running a standard population without date limitation. Search terms for the HEED database are given below (for Cochrane population see F.2).

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Study filter used	Date parameters
Varicose veins	Economic [Embase and Medline]	• 2009 - 17/10/2012 (Medline and Embase) • All years - 17/10/2012 (NHS EED, HTA and HEED)

HEED search terms

1.	AX=varicos* AND vein*
2.	AX=sapheno* AND vein*
3.	AX=venous AND insufficien*
4.	CS=1 OR 2 OR 3

F.4.2 Quality of life reviews

Quality of life (QOL) searches were run in Medline and Embase by combining the standard population with the QOL filter (F.1.5) without date limitation.

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Study filter used	Date parameters
Varicose veins	QOL	All years – 17/10/2012

Appendix G: Evidence tables clinical studies

G.1 Chapter 5 – patient perceptions and expectations

Table 15: Bobridge 2011[27]

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Bobridge A, Sandison S, Paterson J, Puckridge P, Esplin M. A pilot study of the development and implementation of a 'best practice' patient information booklet for patients with chronic venous insufficiency. Phlebology 2011; 26: 338-343	Observational before-after study. Because of the lack of a control group the findings of this study are prone to considerable threats to internal validity. Setting: Australian General Hospital.	30 originally recruited. 3 withdrew due to significant health problems and one withdrew with time management issues. 26 thus started the study. At the 6 month follow-up a further 3 withdrew due to significant health problems and 3 were lost to follow-up: 20 were thus left for analysis at 6 months. This was a per-protocol analysis.	15 women, 11 men; mean (range) age: 71.8 (38-90); CEAP stages: • C3: 11.5%, • C4: 38.5%, • C5: 30.8%, • C6: 19.2%; Current treatment: • compression stockings - 69.2%, • compression bandages – 30.8%, • moisturising skin – 26.1%, • leg exercises – 15.4%, • leg elevation – 3.8%; median 24 month duration of chronic venous insufficiency (CVI) (range 0.25-684 months); most common causes of CVI were superficial and deep perforator incompetence, and superficial great saphenous and deep incompetence (15.4% each); co-morbidities: • hypertension (50%), • type II diabetes (15.4%),	Patients given baseline questionnaires: health Education Impact Questionnaire (HEIQ), measuring the participants chronic venous insufficiency (CVI) knowledge; they were also given the CIVIQ. The patients were then given an information booklet, which had been developed on the best available evidence from the literature; it contained lay term information on the pathophysiology of CVI and the importance of skin care, leg elevation, exercise, diet and compression garments. The information booklet had been amended after consultations with vascular clinicians. A vascular nurse specialist gave the booklet, and explained its contents. The participant was asked to take the information booklet home, to read through the information, and to undertake the recommended best practice activities in their home environment over the next 6 month period. No other intervention was given, though it is assumed (unclearly reported) that	None reported

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
			- thyroid dysfunction (15.4%); - BMI range 20-35.4 (mean 30.8). **Inclusion:** Duplex evidence of reflux, with a CAEP of C3-C6. **Exclusion:** Leg swelling due to cardiac, renal or hepatic dysfunction, lymphodema, lipoedema, DVT, cellulitis, cancer or post-op swelling; diminished mental cognition; physical disability.	patients were allowed to continue their current treatment regimens (as described in patient characteristics column). Further measurements (HEIQ and CIVIQ) were taken at 1 and 6 months post-booklet allocation via the telephone.	

Results: The paper gives descriptive results only. P values given but no event rates.

<u>1 month post booklet implementation (n=26)</u>

There were significant improvements in participants performing at least one activity to improve their CVI (p=0.01), monitoring their CVI (p=0.045), knowing things which could trigger their CVI and make it worse (p=0.005), having effective ways to prevent their CVI symptoms from limiting what they can do (p=0.045). There were also improvements in the ability to travel by car or bus (p=0.05), undertaking social activities (p=0.03) and feeling less embarrassed about showing their legs (p=0.025).

<u>6 months post booklet implementation (n=20)</u>

During the time between 1 and 6 months, there was a significant reduction in the number of people worrying about CVI (p=0.012) and feeling embarrassed about showing their legs (p=0.005), as well as being able to climb several flights of stairs (p=0.008)

At 6 months, there were also significant improvements in performing at least one activity to improve CVI (p=0.003), knowing things which could trigger CVI and make it worse (p=0.016), having effective ways to prevent CVI symptoms limiting what they can do (p=0.008), worrying about their CVI (p=0.03) and feeling a sense of hopelessness about their CVI (p=0.007). there was also a significant improvement in leg and ankle pain (p=0.038), ability to do domestic chores (p=0.017), feeling nervous and tense (p=0.026) and feeling embarrassed about showing their legs (p=0.008).

Table 16: Campbell 2006[41]

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Campbell WB, Decaluwe H, MacIntyre JB, Thompson JF, Cowan AR. Most patients with varicose veins have fears or concerns about the future, in addition to their presenting symptoms. Eur J Vasc Endovasc Surg 2006; 31: 332-334.	Quantitative cross-sectional questionnaire study. Setting: unclear but likely to be a vascular unit in an NHS secondary care trust.	203 patients initially sent in their questionnaires – a 62% response rate. 13 were later excluded due to 8 not having varicose veins, 3 having ulcers and 2 having phlebitis. Hence 190 participated in the study.	Patients referred to a vascular unit with “uncomplicated varicose veins”. 75% female; median age 51 (range 20-83).	Patients who were due to attend the vascular clinic were sent questionnaires beforehand, and asked to bring them in completed for clinic. No reminders were given, and no patient was asked to complete a questionnaire after receiving advice in clinic. The questionnaire contained 13 questions about symptoms and future expectations. The questions relevant to future expectations were: • Have you any other concerns, worries or fears about your varicose veins? Yes/No • If yes, what are they? • Are you worried that your varicose veins might cause you medical harm? Yes/No • If yes, what exactly are you worried about?	None reported

Results:

Negative expectations about prognosis

- 150/190 (79%) reported that they had concerns, worries or fears about their varicose veins:
- 59/190 (31%) feared future thrombosis
- 30/190 (16%) feared future trauma/bleeding
- 28/190 (15%) feared future ulcers
- 22/190 (12%) feared future circulatory disease
- 8/190 (4%) feared future phlebitis
- 57/190 (30%)had general concerns about the future, particularly if there was a family history of varicose veins.

These worries contrasted with the answers to another question on the questionnaire, which asked about their reason for seeking medical advice: only 27/173 (16%) stated concerns about the future.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Methodology</th><th>Source of funding</th></tr>
<tr><td colspan="6">How can these expectations be addressed?
The authors suggested that “good explanation (both verbal and written) about the nature and prognosis of varicose veins should be a routine part of good patient management. Reassurance against the likelihood of a benign prognosis leads many to decide against treatment, especially if they understand they can return in future. We do not know which patients will go on to develop skin problems or ulceration, but clinical experience suggests that the proportion is small and patients should be told the warning signs of eczema or darkening of the skin at the ankle.”</td></tr>
</table>

1 **Table 17: Darvall 2009[65]**

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Darvall KAL, Bate GR, Sam RC, Adam DJ, Silverman SH, Bradbury AW. Patients' expectations before and satisfaction after ultrasound guided foam sclerotherapy for varicose veins. Eur J Vasc Endovasc Surg 2009; 38: 642-647.	Quantitative cross-sectional questionnaire study. Setting: Large NHS secondary care trust	351 patients (464 legs). 80% response rate for the expectations questionnaire.	Consecutive patients undergoing foam sclerotherapy for symptomatic varicose veins. Patients had been referred for treatment by their GPs to NHS vascular surgeons at a single hospital. 35% male; 25% had recurrent disease; 67% had CEAP 2-3; 33% had CEAP 4-6; all had symptomatic primary varicose veins; 97% had superficial venous reflux only and 3% had both superficial and deep reflux; all were secondary to reflux not obstruction. Treatment was for the great saphenous vein (76% of patients), small saphenous vein (10%) and a combination of great saphenous vein, small saphenous vein and anterior accessory saphenous vein (14%).	A questionnaire was given one week prior to foam sclerotherapy treatment. The questionnaire responses were on a 5 point Likert scale (an awful lot, a lot, quite a bit, a little, not at all), which was later collapsed to 3 categories: "a significant improvement", "quite a bit" and "not at all" (the paper uses the term "moderate" in the results section, which presumably means "quite a bit"). The patient could also indicate if a question was not applicable. The questionnaire was given for each leg to be treated (so a bilaterally affected patient would do two questionnaires). **Section 1** asked about the expected improvements in symptoms (pain or aching, itching, tingling, restless legs, cramps, swelling and heaviness). **Section2** asked about expected improvements in appearance, lifestyle (choice of clothes, work performance, social and leisure activities and relationships. [*In addition a post treatment questionnaire was given 6 months after treatment to ascertain actual subjective improvements in all these areas, using the same response categories. Integration of responses from the pre and post treatment questionnaires allowed estimation of whether expectations were met.*]	None reported

Results:

Symptom expectations

A significant improvement in symptoms was expected in approximately 33% of legs, and a moderate improvement in 67%.

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding

[*Depending on the symptom, between 49% and 63% of legs had significant improvement in symptoms at 6 month post-treatment and about 10% had no improvement at all. Overall, expectations were met or exceeded in 80% legs.*]

The detailed expectations data for individual symptoms are given below (the percentage figures are approximate as extrapolated from low resolution table)

Symptom	**Expectation of significant improvement (%)**	**Expectation of moderate improvement (%)**
pain	37	63
itch	32	68
tingling	24	76
cramp	30	70
restless legs	29	71
swelling	37	63
heaviness	37	63

Percentages where pre-operative expectations were not met 6 months post-operatively

	Factor	**Legs [n=365] or patients [n=281] where expectations were not met**
Symptoms	Pain	20%
	Itch	21%
	Tingling	18%
	Cramp	23%
	Restless legs	22%
	Swelling	27%
	Heaviness	18%
Other factors	Appearance of the legs	12%
	Choice of clothes that can be worn	25%
	Performance at work	25%
	Relationships	14%
	Enjoyment of leisure activities	30%

Cosmetic expectations

Over 60% of patients expected a significant improvement in the appearance of their legs (a further 30% expected a moderate improvement).

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
[*96% actually noticed a significant improvement at 6 months.*] **Life-style benefits expectations** Approx. 30% of patients expected significant improvement in the choice of clothes, and a further 40% expected moderate improvement. [*75% of patients met or exceeded these expectations*] Approx. 27% of patients expected significant improvement in performance at work, and a further 40% expected moderate improvement. [*75% of patients met or exceeded these expectations*] Approx. 27% of patients expected significant improvement in leisure activities, and a further 40% expected moderate improvement. [*75% of patients met or exceeded these expectations*] **Relationships expectations** 10% of patients expected significant improvement in relationships, and a further 15% expected moderate improvement. [*>50% actually experienced such improvements.*] **Factors affecting expectations** Cosmetic and social expectations did not depend on whether a patient had had previous varicose veins surgery. Younger age (<55yrs) and CEAP stage C2 disease were each related to higher expectations of cosmetic improvements. Women and C2 patients had higher expectations in terms of clothes choice. Work, relationships and social/leisure expectations were not related to any measured factors.					

Table 18: Dillon 2005[82]

Reference	Study type	No of patients	Patient characteristics	Methodology	Source of funding
Dillon MF, Carr CJ, Feeley TMF, Tierney S. Impact of the informed consent process on patients' understanding of varicose veins and their treatment. Irish Journal of medical science 2005; 174: 23-27	Quantitative questionnaire study carried out in Republic of Ireland. Setting: randomly selected vascular clinics in Republic of Ireland.	82 given the original questionnaire, and all 82 completed it. 67/82 completed the telephone interview 2 weeks post-information provision (pre surgery) and reasons for drop-out are not given.	Patients with newly diagnosed varicose veins referred to randomly selected vascular clinics for surgery. 57 females; median age (range) of 46 (17-72) years; 37/82 had completed secondary education.	The initial written questionnaire was given at the first vascular clinic appointment. It is unclear if this was given before or after the consultation, but, given the questionnaires purpose of evaluating initial expectations, it appears likely it was before the consultation. This because the consultation included an in-depth discussion of the nature and consequences of surgery; furthermore, immediately after the consultation the patient was given a leaflet reiterating this information. This questionnaire assessed the expectations of the outcome of surgery and the perception of threats to health from varicose veins. Two weeks later (but before the surgery itself) the patients were given a repeat of the initial questionnaire (but in telephone interview form in all but one case) to assess the effects of the discussion and leaflet on expectations	None reported

Results:

Expectations about varicose vein risks

- 46/82 initially believed that they were at "high risk" of developing ulcers. Two weeks after information giving this figure was 40/67.
- 41/82 initially believed that they were at "high risk" of developing DVT. Two weeks after information giving this figure was 33/67.
- 26/82 initially believed that they were at "high risk" of bleeding from minor injuries. Two weeks after information giving this figure was 45/67.
- 27/82 initially believed that they were at "high risk" of developing gangrene. Two weeks after information giving this figure was 19/67.

34/82 initially stated that their varicose veins caused them "significant personal anxiety".

Expectations of surgery

(% given for results of telephone questionnaire in paper, which cannot be converted to a fraction due to uncertainty in the value of the denominator)

- 66/82 initially believed that surgery will improve appearance. Two weeks after information giving this figure was 90%.
- 63/82 initially believed that surgery will improve pain. Two weeks after information giving this figure was 84%

Reference	Study type	No of patients	Patient characteristics	Methodology	Source of funding
• 62/82 initially believed that surgery will improve itch. Two weeks after information giving this figure was 80%. • 63/82 initially believed that surgery will improve heaviness. Two weeks after information giving this figure was 86%. • 55/82 initially believed that surgery will improve flares. Two weeks after information giving this figure was 31%. **Other expectations** • 57/72 initially believed that recovery after surgery would take < 2 weeks. Two weeks after information giving this figure was 44/62. • 15/72 initially believed that return to work after surgery would take a month. Two weeks after information giving this figure was 17/62. Recall of complications at the telephone interview was poor – only 18/67 could name any adverse effects. 50/67 remembered getting the educational leaflet, and recall of complications was significantly more likely in those who recalled getting the leaflet.					
Author summary: Patients attending varicose veins clinics have an unrealistic expectation of the benefits of surgery and fail to understand the benign nature of their condition. The outpatient [information-giving] process has little effect on patient-held beliefs.					

Table 19: Palfreyman 2004[199]

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Methodology**	**Source of funding**
Palfreyman SJ, Drewery-Carter K, Rigby K, Michaels JA, Tod AM. Varicose veins: a qualitative study to explore expectations and reasons for seeking treatment. Journal of Clinical Nursing 2004; 13: 332-340.	Qualitative study. Setting: a large NHS secondary care trust in Sheffield.	16 recruited by a research nurse. 22 were approached but 6 were unable to participate due to other commitments. Purposive sampling was used to get patients of both genders, and a range of ages.	Patients who had been referred for varicose vein specialist investigation by their GPs. Reasons for seeking referral from GPs were primarily for relief of symptoms. **Inclusion:** patients with varicose veins who were referred for specialist assessment/treatment. **Exclusion:** Serious complications such as ulcers or bleeding; significant risk factors such as DVT or fractures. **Baseline Characteristics**: 3 males and 13 females; age from 20-76; length of time with varicose veins 4-51 years; previous treatments were none (n=7), compression (n=6), surgery (n=2), sclerotherapy (n=1). The treatment outcome was surgery (n=13) and conservative treatment (n=3).	Interviews were conducted 5-14 days after attendance at a surgical outpatient clinic. Interviews were semi-structured and conducted in a quiet room within the hospital setting. The interviews were tape-recorded and lasted 30-45 minutes. The anonymous and transcribed transcripts were entered into a qualitative software package (qrsNVIVO). Framework analysis used to identify thematic frameworks. Trustworthiness of the data was reported as "ensured" by the use of: • framework analysis • on-going reflection and discussion amongst researchers (but no mention of formal triangulation methods) • Interpretation of emerging issues were tested by feedback to the patient during the interview • Analysis and interpretation from earlier interviews were tested in subsequent interviews • The anonymous transcripts and key themes were shown to a subset of interviewees to check validity of findings	Northern General Nursing and PAMs Research Grant – no conflict of interest likely.
Results:					
<u>Expectations</u> <u>Positive expectations</u>					

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Positive expectations of treatment effects on the level current symptoms Patients generally had an expectation that something could be done about their symptoms. "…more than anything is that it won't be as it is now, so that the pain factor, the heaviness, everything that goes with it hopefully will have gone…" Although an expectation of cosmetic improvement was also present, this expectation was not the main reason for seeking treatment. **Positive expectations of prognosis if treated** There was an expectation that surgery would prevent future deterioration of symptoms and extent of varicose veins. Patients either had the expectation of no possibility of recurrence, or that even a short symptom free period would be worth it. Even those with previous surgery expected that their surgery this time would work better, and that even a short symptom free period would be worth it. Negative expectations **Negative expectations of prognosis if untreated** An important motivation for treatment was that DVT and ulceration could occur later because of their varicose veins. A particular concern was that varicose veins might exacerbate the risks of developing a DVT whilst flying. **Negative expectations about adverse events of surgery** Fear of surgery was common: "….I'm in the middle now. I'm frightened of having them done and I'm frightened of having them…." **How can these expectations be addressed?** Consideration of patient expectations should influence the nature of the nurses' assessment and information giving.					
Author's summary: "….they had actively sought treatment from the health service, with the expectation that they will gain symptom relief…this wish for their symptoms to be relieved by treatment might be an unrealistic expectation, as the evidence suggests that surgery in particular may not have any effect on the symptoms experienced in the leg with varicose veins……The patients, in seeking to relieve their symptoms, were after an immediate benefit. This belief meant that they disregarded the potential risks of treatment… the participants were also being unnecessarily anxious about the complications of varicose veins….such worries were not supported by the evidence….patients over-estimate the extent to which the appearance of their legs can be improved by treatment….."					

Table 20: Shepherd 2010[247]

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Shepherd AC, Gohel MS, Lim CS, Hamish M, Davies AH. The treatment of varicose veins: an investigation of patient preferences and expectations. Phlebology 2010; 25: 54-65.	Cross-sectional questionnaire survey. Setting: vascular clinic in an NHS secondary care trust.	111. 83 gave complete responses and the remaining 28 gave partial responses.	Consecutive patients referred to one consultant vascular surgeon with symptomatic varicose veins; 73% of patients were female; 43% were unemployed, and 17% were part-time employees; age range 18-83; reported co-morbidities were: • hypertension - 16% • previous deep vein thrombosis – 7% • asthma – 5% • diabetes – 4% • epilepsy - 2% • Chronic obstructive pulmonary disease (COPD) – 2% • Ischeamic heart disease (IHD) – 2% • Transient ischaemic attacks (TIAs) – 1% • No co-morbidities – 61%	Patients were invited to complete an anonymous questionnaire prior to their consultation (and prior to any information being given out). Questions related to occupation, physical symptoms and impact of the varicose veins, patient knowledge of existing treatments, concerns about complications and recurrence, preferred treatment options and factors that might influence decisions regarding treatment.	None reported

Results:

Negative expectations about varicose veins treatments

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
The main concerns that patients had about treatment were presented in a low resolution figure, and so exact data are unclear. However, it appears that about 35% were “extremely concerned” about recurrence, and about 16% were “extremely concerned” about discomfort after treatment **Awareness of treatment options** • 86% aware of surgery as an option • 32% were aware of laser ablation • 22% were aware of sclerotherapy • 18% were aware of radiofrequency ablation. • 10% were unaware of any treatments. 24/103 expressed a preference for endovenous treatments (i.e. endothermal ablation or foam sclerotherapy) over surgery. Of the endovenous treatments, laser was the most popular (first choice of 11%). Most patients (74/103) stated that they didn’t know enough to express a treatment preference.					

1

Table 21: Zubilewicz 2009[290]

Reference	Study type	No. of patients	Patient characteristics	Methodology	Source of funding
Zubilewicz R, Chmiel-Perzynska I, Derkacz M, Schabowski J. The women's span of knowledge about chronic venous disease. Family Medicine and Primary Care Review 2009; 11: 919-922.	Cross-sectional survey. Setting: Poland but no other details provided.	156	Polish women with chronic venous disease (CVD) who had never been treated. Average age was 44.5 (16) years. 19% were <30 years old, 68% were between 31-65 years old and 13% were over 65 years old. 14% had primary education, 47% secondary education or vocational training and 39% had a university degree.	Participants were given a multiple choice questionnaire, which was aimed to assess knowledge concerning modifiable risk factors for chronic venous disease and the presence of symptoms. No other details given.	None reported

Results:

<u>Expectations / preconceived ideas about modifiable risk factors</u>

The following were the most often suggested risk factors for chronic venous disease. The figures given are the percentage of participants believing it was a risk factor:

- Overweight and obesity (85%)
- High heeled footwear (73%)
- Standing and sitting postures at work (71% and 61% respectively)
- Pregnancy (58%)
- Crossing legs (51%)
- Long journeys by car or plane (40%)
- Oral contraceptives (30%)
- Use of depilatory wax (17%)
- Under-floor heating (11%)
- Physical activity (20%)

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Methodology</th><th>Source of funding</th></tr>
<tr><td colspan="6">>50% of respondents of <65 years assessed CVD as a severe disorder which lessened Quality of Life (QoL). Approximately 70% of women >65 years considered CVD as especially serious.
33.3% were aware that CVD was a risk factor for ulceration.
Approximately 70% of women under 30 years regarded CVD as primarily a cosmetic problem.
The perception of CVD as a serious disease was higher in those with lower educational attainment.</td></tr>
</table>

G.2 Chapter 6 – referral from primary care

G.2.1 Risk factors associated with disease progression

Table 22: Boccalon 1997[28]

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Boccalon H, Janbon C, Saumet JL, Tafani A, Roux T, Vilain C. Characteristics of chronic venous insufficiency in 895 patients followed in general practice. International Angiology 1997; 16: 226-34	Cross-sectional, but contained potentially useful gender and existence of previous thrombus aetiology findings which will also be effectively case-control.	895, drawn from all regions of France. These included 229 who were asymptomatic and without any detectable signs. These 229 are not included in this review analysis.	Chronic venous insufficiency of lower limbs, all of which had been treated with 2 months of daily 1g microflavanoid fractions. **Inclusion:** >18; at least one symptom from heaviness, pain or night cramps attributable to CVi for at least 1 year; worsened by prolonged standing or sitting, warmth, and improved by elevation, activity or compression; functional discomfort had to be at least 40/100 on a VAS. **Exclusion:** arteriopathy or neuropathy of the lower limbs.	Gender Age Secondary aetiology	Development of skin changes or ulcerative changes, in terms of being categorised in the three groups: Group 1: no skin changes; group 2: hyper-pigmentation with no ulceration; group 3: more severe skin changes (included “pre-ulcerative*” changes or ulceration). *not explained further.	NA	Not stated
Results:							
Gender Group 1 had 33 men (age 51) and 278 women (age 44); group 2 had 25 men (age 54) and 269 women (age 53) and group 3 had 12 men (age 59) and 49 women (age							

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding

67).

For each group, the % of men and women were:

	Group 1 (<C4)	Group 2 (skin changes not including pre-ulceration or ulceration)	Group 3 (more severe skin changes including pre-ulceration or ulceration)
men	47.1%	35.7%	17.1%
women	46.6%	45.1%	8.2%

<u>Secondary aetiology</u>

The percentage with secondary CVI were: group 1: 3.2%; group 2: 9.9%; group 3: 27.9**%.** The paper reported that a previous episode of DVT was more commonly reported in the history of patients with the most severe objective signs and that this was significant (p<0.001).

<u>Age</u>

The severity increased with age. Gp 1 were 45 (14) yrs, group 2 were 53 (15) yrs and Group 3 were 65 (13) years.

<u>Other factors</u>

Other factors were considered but they were cross-sectional and so do not indicate prognosis for progression.

1 **Table 23: Pannier 2011**[202]

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Pannier F, Rabe E. progression of Chronic Venous Disorders: Results from the Bonn Vein Study. Journal of Vascular Surgery 2011; 53: 254-255	Prospective cohort study	3072 enrolled at baseline. 1978 remained in the study at follow-up. (These were a cross-section of all people, as varicose veins were not an inclusion criterion). The relevant figure is 290, however, as this represents the number with C2 at baseline (and who also attended at follow-up). 432 had C2 at baseline, indicating very high attrition of 142 participants. Reasons for attrition not reported.	Participants were sampled randomly from the population aged 18-79 years living in Bonn and two rural townships. 3072 represented a response rate of 59%. The age and gender were representative of the general German population. **Inclusion:** 18-79 years; German nationality. [Note varicose veins or CVI were not an inclusion criterion] **Exclusion:** hemiparesis/leg amputations; severe illness; moribund patients; systemic inactivating disease. **Baseline Characteristics:** For those attending at baseline, • 56.2% were male, • 33.6% were 18-39 years, • 37.4% were 40-59 years and • 29% were 60-79 years. • 43.9% had a BMI of <25. • 9.6% were C0, • 59% were C1, • 14.3% were C2,	A standardised questionnaire was used to collect information at baseline on the following risk factors: • sociodemographic status • smoking • alcohol • physical activity • blood pressure • medical history • quality of life • hormonal intake • contraceptive pill • professional stress/ work strenuousness • BMI • Heaviness • Feeling of tension • Swelling feeling • Pain during prolonged walking • Itching	Progression from C2 to C3-6 over the 6.6 years	6.6 years	Not stated

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Risk factors studied**	**Outcome measures**	**Length of follow-up**	**Source of funding**
			• 13.55 were C3, • 2.9% were C4 and • 0.7% were C5-6. • 62.4% lived in urban areas. No information reported on the characteristics of the 290 relevant C2 participants remaining at 6.6 year follow-up.				

Results: ** These data has been removed as it is academic in confidence

Risk factor	**RR (95% CI) of the progression from C2 to C3-6**
** These data has been removed as it is academic in confidence	

Table 24: Robertson 2009[230]

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
Robertson L, Lee AJ, Gallagher K e al. Risk factor for chronic ulceration in patients with varicose vein a case contro study. J Vasc Surg 2009; 49:1490-8	Case control study, but cross-sectional analyses included a well (see risk factor studied section). Potential confounders such as socioeconomic status were matched, and othe confounders were adjusted for. The patients were recruited from the same source, and s any bias arising from one group having a systematically higher chance of having any risk factor were reduced. No efforts to ensur optimal recollectio of past exposure.	381 patients were invited to participate. Of these 38 cases and 103 controls di not respond or refused tc participate, leaving 240. This represents a respons rate of 63%. 120 were C6 or C5*[cases]. Of these, 24 had had previous surgery Mean age of first developing an ulcer was 56 (15.5) years [approx 8 years prior to study, on average] – this means any retrospective recollection of <8 years previously would be unlikely to be representative of true "causes". Median (IQR) of 2(1-3) active episodes, each of a mean (sd) duration of 7(13) years. 120 were C4 or less [controls]. Only one leg per subject	All subjects were recruited from the register of venous patients scanned in a vascular laboratory a a large Scottish NHS trust, as well as GP practices in a Scottis region. The cases were to have an open or healed ulcer (C5/6), and the ulcer was to have been active for at least 8 weeks. Subjects with ulcers on the feet were excluded to avoid including diabetic or peripheral vascular diseasePVD patients The controls were selected to have no history of leg ulcers. 16 patients had C1 disease only (10	Many "risk factors" in this study were measured cross-sectionally. The only cross-sectionally measured risk factors that did not present doubt about the direction of cause-effect (if any), and were thus potentially informative, were gender, height and age (these could no possibly be effects of ulceration, and therefore were a cause, or correlating with another, causative, factor). In contrast, cross-sectionally measured factors where the cause-effect directio (if any) was intrinsically unclear were: BMI, weight, blood pressure, venous pump power, ABPI, and existence of reflux in various veins (these could be effects as well as causes). Smoking in the past year and activity in the past year could be regarded as possibly cross-sectional as many of those in the ulcer group are likely to have had ulcer beginning more than a year before. Some factors were measured by asking the patient about past exposure to risk factors, and were therefore potentially informative. Such risk factors were physical activity between the ages of 3 and 45 and daily activity between the	Developmen of ulceration versus no ulceration.	Unclear, as patients were simply asked to recollect activity data when aged 35-45 years – the time duration bac to this would have varied widely, and some patients ma not have even reached this age range.	None

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
	Poor attempt to ensure direction of any cause-effect was unambiguous. No reports of blinding of assessors. Overall, very low quality.	was used. If a patient wer bilaterally affected, only the worse affected leg wa chosen for inclusion. * For those that are C5, it is possible that they were C6 before any of the retrospective recollections. It is thus unclear whether this paper meets inclusion criteria.	cases and 6 controls but were kept in the analysis on the basis that they formed a small percentage	ages of 35 and 45. However, a small proportion (probably <25%) of patients were within those age groups at the time of assessment and so, for those patients, these measures were cross-sectional. The cause-effect status of smoking history was fairly clear given that the mean pack years were around 16. Pre-ulcer weight was another informative factor. Cause-effect was unclear for previous history of DVT/PE or phlebitis as it was very unclear whether these were antecedents of ulceration, or merely an uncongenial accompaniment. All ORs were adjusted for age and sex.			

Results. <u>ONLY results that pertain to risk factors that are likely to have preceded ulceration are included</u>. Cross-sectional data (except for those where the possible direction of cause-effect is fixed, such as gender) are not included as they are of no relevance to the issue of prognosis. Relevant univariable results (only adjusted for age and sex) are given below.

Multivariable results are not given as no potentially prognostic factors remained in the model after stepwise removal. All the results presented here are univariate results

Risk factor	**mean (sd) RF in case / % with RF**	**mean (sd) of RF in controls/ % with RF**	**P value**
Age	64.1(13.4)	59.9(11.7)	0.01
% male	55%	43%	0.07
Risk factor	**mean (sd) RF in case**	**mean (sd) of RF in controls**	**OR (CI) [univariable in terms of no adjustment for other RF, except age and sex]^{b}**

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
height		1.67(0.11)	1.67(0.1)	0.54(0.02-19.41)			
Smoking pack years		4.47 (3.16-6.32)	4.1(2.45-5.48)	1.08(0.9-1.29)			
Risk factor		**%with the RF in case**	**% with RF in controls**	**OR (CI) [univariable in terms of no adjustment for other RF, except age and sex]**[b]			
Physical exercise in past year[a]							
Nil		28.8	14.9	Reference			
Light		35.6	42.1	0.44(0.21-0.91)			
Mod		28.2	36.8	0.43(0.20-0.93)			
Strenuous		6.8	6.1	0.70(0.20-2.41)			
Physical exercise aged 35-45							
Nil		15.3	14.0	Reference			
Light		28	28.9	0.86(0.37-2.01)			
Moderate		39.8	44.7	0.76(0.34-1.68)			
Strenuous		16.9	12.3	1.29(0.48-3.49)			
Daily activity in past year[a]							
sitting		35.6	17.5	Reference			
walking		48.3	60.5	0.43 90.22-0.820			
light loads		7.6	15.8	0.29(0.11-0.77)			
heavy work		8.5	6.1	0.99(0.29-3.35)			
Daily activity aged 35-45							
sitting		16.1	14.9	Reference			
walking		47.5	44.7	1.09(0.49-2.41)			

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
light loads		14.4	18.4	0.79(0.31-2.03)			
heavy work		22.0	21.9	0.86(0.35-2.10)			
Risk factor (RF)		**%with the RF in case**	**% with RF in controls**	**P value**			
History of phlebitis		37	28	NS			
History of leg fracture		18	11	NS			
History of arthritis		40	35	NS			
Ever smoked		63.6	45.6	0.009			

(a) Unlikely to have preceded ulceration but included for completeness

(b) The OR is the odds ratio of ulceration for every additional increment of the continuous variable [adjusted for age and sex]

Table 25: Scott et al. 1995[242]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Risk factors studied</th><th>Outcome measures</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Scott TE, LaMorte WW, Gorin DR, Menzoian JO. Risk factors for chronic venous insufficienc y: a dual case-control study. J Vasc Surg 1995; 22:622-8</td>
<td>Case control study, with cross-sectional components.

Potential confounders suc as socioeconomic status, age, BMI etc were not matched. A multivariable analysis was performed that adjusted for these confounders, and it is included in this review as i predominantly contains risk factors that are potentially preceding ulceration.

The patients were recruited from the same source, and so any bias arising from one group having a systematically higher chance of having any risk factor were reduced.

No efforts to ensure optimal recollection of pas exposure.

Assessor performing the retrospective survey was</td>
<td>129 with varicose veins and 93 with chronic venous insufficiency “CVI”. All those with CVI had ulceration. There was also a group of subject with no venous disease (used to assess risks for <i>initially developing</i> venous disease, so not relevant to this review question) that is not included here.

Rates of refusal were described as <5% and to b the same across the groups.</td>
<td>Exclusion: <18 years; unable to speak English; unable to give informed consent.

Cases: Patients with class II or class III CVI, cared for in vascular surgery clinics at a large medical centre in the USA. Unclear if all had ulcers, but elsewhere in the paper they are described as having ulceration. Diagnosis based on visible appearance.

Controls: Patients with varicose veins, attending the same clinic as the cases.
<table>
<tr><th></th><th>CVI (with ulceration)</th><th>varicose veins</th></tr>
<tr><td>Age</td><td>59(1.6)</td><td>43.7(1.3)</td></tr>
<tr><td>BMI</td><td>30.4(1)</td><td>25.6(0.5)</td></tr>
<tr><td>Male</td><td>58%</td><td>17.8%</td></tr>
<tr><td>%white</td><td>51.6%</td><td>70.6%</td></tr>
<tr><td>Mean estimated family income in US$ (sd)</td><td>25990 (1080)</td><td>31825 (1398)</td></tr>
<tr><td>college education</td><td>27.3%</td><td>52.6%</td></tr>
<tr><td>lack of insurance</td><td>33.7%</td><td>19.4%</td></tr>
</table>
</td>
<td>Retrospective information on potential risk factors was done via a structured interview, by an interviewer blinded to the status of the patients.

These included medical history, years of smoking, standing at work and exercise levels. Of these, standing at work and exercise were cross-sectional and so not included in this review.</td>
<td>Existence of ulceration</td>
<td>Unclear. The only retrospective questions were medical history and years smoked, and the distance back into the past these variables occupied was unspecified.</td>
<td>None stated</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Risk factors studied	Outcome measures	Length of follow-up	Source of funding
	blinded to the group statu of the subjects. Overall, very low quality.								

Results: ONLY results that pertain to variables that are likely to have preceded ulceration are included. Cross-sectional data (except for those where the direction of cause-effect is fixed, such as gender) are not included as they are of no relevance to the issue of prognosis. Relevant univariable results (only adjusted for age and sex) are given below.

Risk factor	**CVI %**	**Varicose vein %**	**Significant difference? (p values not stated)**
History of heart disease	22.6%	4.6%	Y
History of diabetes mellitus	22.6%	2.3%	Y
History of hypertension	49.5%	16.3%	Y
History of kidney disease	4.4%	2.3%	N
History of arthritis	19.7%	13.9%	N
History of leg injury	54.8%	17.8%	Y
History of phlebitis/clot	45.6%	24.2%	Y
History of oral contraceptive use	5.1%	20.7%	Y
years smoked	17 (1.7)	8.8(1.0)	Y
Multivariable analysis results			
Risk factor	**OR for ulceration**		
age	1.07/yr (1.04-1.1)		
male sex	8 (3.5-18.3)		
BMI	1.07/kg/m^2(1.01-1.13)		
no health insurance*	3.2 (1.3-7.7)		
history of leg injury	4.7 (2.1-10.5)		
Diabetes mellitus	4.3 (0.99-18.7)		

1
G.2.2 Factors associated with response to treatment

2
Table 26: Fischer 2006[98]

Reference	Study type	No of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Fischer R, Chandler JG, Stenger D, Puhan MA, De Maeseneer MG, Schimmelpfennig L. Patient characteristics and physician-determined variables affecting saphenofemoral reflux recurrence after ligation and stripping of the great saphenous vein. J Vasc Surg 2006; 43: 81-7	Prospective observational study. Main aim was to evaluate modifiers of treatment success.	n=1261 patients /1638 limbs. Unspecified attrition, but sophisticated imputation used.	Patients undergoing SFJ ligation and GSV stripping, from 1978 to 2003. **Inclusion:** Primary operations **Exclusion:** History of DVT, or serious trauma to the affected leg; procedures involving crossectomy but not GSV stripping. **Baseline Characteristics:** Mean age 49.7(12) at the time of operation	BMI, prior parity, interim pregnancy, deep venous insufficiency, age, gender, side affected, diabetes mellitus.	Saphenofemoral reflux recurrence, using duplex, but, in earlier cases continuous wave doppler. Reflux had to last >0.5 seconds.	Variable. All follow-ups were after 1991. Categorised as 2-6 yrs, 7-12 yrs and > 12 years. follow-up duration was normalised through adjustment in the multivariable analysis. Mean was 6.6(4.3)yrs.	

Results:

BMI>29, prior parity, and interim pregnancy were all associated with an increased odds of reflux recurrence. The table below shows the results of the multivariable logistic regression, with odds for recurrence of SFJ reflux recurrence at a mean of 6.6 years shown for relevant patient-related variables.

Variable	OR (95% CIs)
BMI >29 at baseline (compared to $\leq$29)	1.65(1.12,2.43)
Prior parity (compared to none)	2.69(1.45,4.97)
Interim pregnancy (compared to not)*	4.74(2.47, 9.12)

*not a variable that can predict treatment efficacy at the pre-treatment stage, so excluded from results in review.

3

1

Table 27: Gibson et al. 2007[103]

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
Gibson KD, Ferris BL, Polissar N, Neradilek B, Pepper D. Endovenous laser treatment of the short saphenous vein: efficacy and complications. J Vasc Surg 2007; 45: 795-803	Prospective consecutive enrolment of patients. Main aim was to evaluate treatment success and modifiers of AEs.	n=187 patients/210 legs. High (40%) attrition by the stage of the final follow-up (2-11 months).	C2-6 patients undergoing EVLA	Anatomic patterns of the SSV. Type A was a SPJ with no significant branches; type B was a SPJ with a large extension Giacomini vein; type C was a SPJ or SFJ with no direct termination into a deep vein, and the SSV continued as a Giacomini vein above the popliteal fossa. Author's own classification system. Also: gender, leg side, preoperative presence of ulcer, pre-op presence of stasis, pre-op presence of pain, and age.	Incidence of the adverse event of DVT at 2-4 days (but unclear) Recanalisation at 2-11 months (but unclear)	4-10 months	None stated

Results:

<u>DVT risk factors</u>

SSV anatomy had an association with DVT incidence. The risks of DVT for each group were as follows: Group A: 10/88 (11.4%); Group B: 2/69 (2.9%); Group C: 0/52 (0%). Specifically, a SPJ with no significant branches (Type A) carried a trend (p=0.07) for a higher risk than type B [type B compared to type A, for risk of DVT: OR:0.23(0.05, 1.10)]. There were no DVT cases in type C, so no ORs could be produced, but the Fisher exact test showed that type C had a significantly lower risk than type A (p=0.013).

No multivariable results are given, but this is because the only variable that had a p<0.1 on univariate testing was SSV anatomy type. Hence no variables other than SSV

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
anatomy type would have been put in the multivariable model – hence the univariable results for SSV anatomy type are the full results. For completeness, all univariable results are given below:							

Risk factor for DVT (reference given in brackets)	**OR (95% CI) for DVT at variable time (adjusted for time)**
right side (compared to left)	0.64(0.20, 2.09)
stasis (compared to no stasis)	0.46 (0.1, 2.16)
Age (per 10 year increment)	0.99(0.62,1.57)
Anatomy type B (compared to type A) [there were no DVT cases in type C, so no ORs could be produced]	0.23(0.05, 1.10)
Gender	0/28 DVTs in men, 12/182 DVTs in women, p=0.4*
Pre-op ulcer	0/11 DVTs in those with ulcers, 12/199 DVTs in those with no ulcers, p=0.5*
Pain	0/13 DVTs in those with pain, 12/197 DVTs in those with no pain, p=0.5*
ulcer, stasis or pain	0/11 DVTs in those with ulcers, stasis or pain 12/199 DVTs in those with no ulcers, stasis or pain , p=0.5*

Recanalisation risk factors

A logistic regression analysis using the same risk factors was carried out to evaluate their effects on the odds of recanalisation. No results were reported, other than that none of the variables had a significant relationship with recanalisation.

1 **Table 28: Gonzalez-Zeh et al. 2008**[107]

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
Gonzalez-Zeh R, Armisen R, Barahona S. Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one year follow-up results. J Vasc Surg 2008; 48: 940-6	Non-randomised trial with main aim of comparing 2 treatments, but with logistic regression analysis included to assess effects of potential treatment modifiers. Only one limb per patient was included and treated in this study. A single surgeon with experience of 800 EVLA s and 2000 foam sclerotherapies did both interventions. Patients were not allowed to mix, to avoid contamination of patient expectations. Clinical and	98. No patients dropped out and all followed up.	C2-6 patients undergoing EVLA and foam sclerotherapy. Patients were allowed to choose between foam sclerotherapy and EVLA, and they were told the efficacy of each was equivalent. **Inclusion:** Primary incompetence of the GSV and SFJ insufficiency with a reflux time of 0.5 seconds measured over a distance of at least 20cm in the upper leg. **Exclusion:** pregnancy; active thrombophlebitis, clotting disturbances; thrombophilia or coagulation disorders; History of DVT; history of malignancies. **Baseline characteristics:** Despite the lack of randomisation the groups were well matched.	Clinical grouping (C1-6), pre-op VCSS, age, pre-op GSV diameter	Presence of reflux, as measured by duplex.	1 week, 1 month, 6 months and 1 year.	Not stated

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
	ultrasound follow-ups done by an assessor blinded to treatment, but probably not to baseline predictors.						

Results:

Subgroups analysis showed that a larger pre-op GSV diameter was associated with reflux in both the foam and EVLA treatments. Veins <6.5cm have a 90% success rate with foam, and veins <12mm have a 90% success rate with laser.

Logistic regression analysis showed that for each treatment, pre-op GSV diameter (?>12mm, unclear) was the only factor significantly predicting reflux. The multivariable results for each treatment separately are given below. The OR(95% CIs) are for the odds of reflux. The analysis is unclearly reported. The reference values for categorical variables (Clinical groups, GSV diameter) are unclear. It is likely that the reference value of GSV diameter is <12mm (therefore the variable below is given as GSV >12mm). Though not stated it is likely that the ORs for the continuous variables (age, VCSS) are per increment increase in the variable.

Variable	**Foam sclerotherapy**	**laser**
clinical groups C1-6	0.89(0.39-2.20)	2.87(0.33-24.77)
VCSS	0.97(0.44-2.15)	0.31(0.03-3.12)
Age	0.99(0.91-1.08)	0.94(0.79-1.09)
GSV diameter (>12mm?)	1.68(1.24-2.27)	1.91(1.02-3.59)

Table 29: Islamoglu 2011[122]

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
Islamoglu F. An alternative treatment for varicose veins: ligation plus foam sclerotherapy. Dermatol surg 2011; 37: 470-479	Prospective non-randomised study. Patients were allowed to choose treatments. The main aim was the comparison of stripping versus foam sclerotherapy and crossectomy, but in the absence of a differential treatment effect most of the results sections focus on the non-treatment predictors of treatment success/failure.	372. No mention of drop-outs. Unclear if the sample were defined by completers only.	C2-6 patients undergoing foam sclerotherapy with crossectomy or classic stripping. All done by the same surgeon. Mean age 48.6(10.1). 159/372 male. 156/372 in sclerotherapy group. All symptomatic. Bilateral in 51 subjects. **Inclusion:** GSV reflux; C2-6; primary aetiology. **Exclusion:** pregnancy; sclerosant allergy; acute thrombophlebitis; acute DVT; local infection; immobility.	Unilateral/bilateral, pre-operative CEAP, employment, familial predisposition, gender, DVT, age, pre-operative deep venous insufficiency (DVI), pre-operative perforator incompetence (PI).	Symptom recurrence, post-operative CEAP, post-operative Perforator incompetence.	6 months, and at further 6 month intervals (mean follow-up was 10.2 (5.1) months.	Not stated

Results

Multivariable results only, all adjusted for treatment type (always NS in all analyses) as well as other variables. The time of follow-up is unclear, but presumably 6-12 months.

<u>Post-op symptom recurrence</u>

These results were poorly reported by the paper. The directions of the ORs in the text do not tally with the raw data for the unilateral/bilateral variable. The direction of effect given below is that determined by the raw data. ORs are for the existence of post-operative symptom recurrence.

Variable	OR (95% CIs)
unilateral (versus bilateral)	2.376 (1.682-3.356)

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
Pre-op CEAP ≥3 (versus <3)		3.298(1.897-5.731)					
No job (versus a job)		0.133(0.073-0.243)					
No family history (versus a family history)		0.357(0.198-0.643)					
<u>Post-op CEAP < 3</u> Again, poorly reported. ORs are for post op CEAP <3							
Variable	**OR (95% CIs)**						
unilateral (versus bilateral)	2.497(1.337-4.663)						
Pre-op CEAP <3 (versus ≥3)	1.445(0.368-4.818)						
male (versus female)	1.542(0.201-3.355)						
No previous DVT (versus previous DVT)	2.827(0.831-9.619)						
Age <60 (versus >60)	1.215(0.262-4.012)						
Post-op perforator incompetence							
Age >60 (compared to <60)	23.618(8.423-66.223)						
Pre-op CEAP >3 (compared to <3)	2.741(1.174-6.401)						
No job (compared to employed)	0.112(0.039-0.317)						
Family history (compared to none)	2.927(1.020-8.398)						
Pre-op PI (compared to none)	6.102(2.214-16.815)						
There was also a multivariable analysis evaluating which factors were associated with earlier (<1 year) or later symptom recurrence, amongst the sub-group with symptom recurrence. Results of this have not been included in this review because they are outside the scope of the review question.							

Table 30: McKenzie et al. 2002[156]

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding
McKenzie RK, Lee AJ, Paisley A et al. Patient, operative and surgeon factors that influence the effe of superficial venous surgery or disease-specific quality of life. J vasc Surg 2002; 3(896-902	Prospective study c consecutive unselected patients aiming to look for factors influencing disease-specific quality of life. This included patient factors, as well as operative and surgeon factors.	203. No mention of drop-outs. Unclear i the sample were defined by completers only.	C2-6 patients undergoing GSV, SSV o SEPS surgery. GSV surgery comprised flus SPJ ligation, stripping c the GSV in the thigh an multiple stab avulsions SSV surgery comprised SPJ ligation and multip stab avulsions; SEPs wa done with a single port technique.	age, gender, pre-operative AVVSSS (high = worse), CEAP grade, first time/recurrent, History of DVT. In patients with bilateral disease, the factors entered into the analysis were those for the worst affected leg.	Post-operative AVVQ	6 months/ 2 yea	None stated.

Results:

6 months multivariable

A higher baseline AVVQ, baseline recurrent disease and baseline CEAP 4 disease predicted higher (worse) AVVQ at 6 months. This model explained 60% of the total variation in AVVQ at 6 months. Square root used to normalise the distribution of baseline AVVQ (Log not possible as raw scores included zero)

Factor	Parameter estimate	SE	t	p
square root of baseline AVVQ	0.57	0.07	7.78	<0.001
primary/recurrent procedure	0.45	0.17	0.15	0.009
CEAP 4	0.39	0.17	0.14	0.026

2 years multivariable

A higher baseline AVVSS and baseline CEAP 5 disease predicted higher (worse) AVVQ at 2 year. In contrast, previous GSV surgery predicted a lower AVVQ. This model explained 47% of the total variation in AVVQ at 2 years. Square root used to normalise the distribution of baseline AVVQ (Log not possible as raw scores included zero)

Factor	Parameter estimate	SE	t	p
square root of baseline AVVQ	0.47	0.08	6.16	<0.001

Reference	Study type	No. of patients	Patient characteristics	Patient-related risk factors studied	Outcome measures	Length of prospective follow-up / retrospective recollection	Source of funding

GSV surgery	-0.73	0.31	-2.35	0.02
CEAP 5	0.62	0.28	2.19	0.030

1

Table 31: Myers 2007[180]

Reference	Study type	No of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Myers KA, Jolley D, Clough A, Kirwan J. Outcome of ultrasound-guided sclerotherapy for varicose veins: medium-term results assessed by ultrasound surveillance. Eur J Vasc Endovasc Surg 2007; 33: 116-121	Prospective observational study. Main aim was to evaluate modifiers of treatment success.	489 patients (677 limbs). Time to event study so attrition catered for in analysis.	**Inclusion:** C2-6 patients undergoing ultrasound guided sclerotherapy (mainly foam but some liquid). Some of these were given over 3-4 separate sessions. **Exclusion:** Previous EVLA **Baseline Characteristics:** Age range 19-92 (median 53); women: 401/489; C2-3 in 90%; 115 limbs were recurrent and the rest were first-time.	Type of vein, age, gender, diameter of GSV, side, CEAP grade.	Time to failure was the outcome. Treatment success defined as persistent occlusion or absence of reflux in treated veins – assessed by ultrasound (unclear if duplex). Time to failure was therefore the duration between the first treatment session (out of the 1-4) achieving full success and the first follow-up when reflux was noted.	Every 3-5 days after each of the 1-4 sclerotherapy sessions; then at 6 weeks; and then at 6 months for 2 years; and then annually.	Not stated

Results: A multivariable cox-regression analysis was carried out for factors influencing failure in all saphenous veins. The table below summarises the results, with a higher HR indicating a greater risk of failure at any point in time compared to the reference category. Younger age and larger (>6mm) diameter GSV were associated with a worse outcome.

Variable (and reference category)	Index category of variable	n	Hazard Ratio (95% CI)
Age (compared to 50-59)	<40	93	**2.16(1.27,3.66)**
	40-49	121	1.11(0.69,1.78)
	60-69	118	1.22(0.79,1.89)
	70+	87	0.63(0.35,1.14)
Sex (compared to female)	Male	112	1.31(0.88,1.94)

Reference	Study type	No of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Side (compared to left)		Right	313	1.19 (0.89, 1.57)			
Vein (compared to GSV)		SSV	174	1.58(1.11, 2.24)			
CEAP (compared to C2/3)		C4/6	62	1.57(0.91, 2.73)			
vein diameter (compared to <5mm)		5 mm	152	1.27((0.79,2.03)			
		6mm	152	2.07(1.35, 3.18)			
		>6mm	112	2.22(1.4, 3.5)			

1 **Table 32: Thomasset 2010[268]**

Reference	Study type	No of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Thomasset SC, Butt Z, Liptrot S, Fairbrother BJ, Makhdoomi KR. Ultrasound guided foam sclerotherapy: factors associated with outcomes and complications. Eur J Vasc Endovasc Surg 2010; 40: 389-392	Prospective cohort study.	116 patients, having 126 procedures. Appears to have very high attrition, as only 116/235 eligible patients attended follow-up. These could have included the worst (or best) responders. But how many of these eligible patients were actually recruited in the first place? Very unclear. Unclear if analysis was by procedure (n=126) or patient (n=116), but likely to be the latter, as there would probably only have been one outcome assessment per person, and thus one analysis (for example if a patient had two UGFS procedures, the second would be a top up and a single outcome would relate to both).	53 men, 63 women. Median age was 55 (range 18-80). Target veins were the GSV (n=75), SSV (n=13), and accessory GSV (n=8). Others involved other veins or more than a single target vein (n=30).	Gender Previous surgery Sites of injection Maximum concentration of sclerosant Pre-procedure CEAP Compliance with post treatment compression Age Volume of sclerosant	Successful outcome – complete occlusion of the target vein on duplex analysis on follow-up. Existence of any complications Existence of each complication analysed separately (superficial thrombophlebitis, pain, skin staining, DVT, allergy and skin blistering)	3 months minimum	None.

Results: Analysis was poorly reported though it seems univariate analyses for the 8 risk factors were performed. Although this study did therefore not meet the inclusion criterion of having a multivariable analysis, because only one risk factor was significant on univariate testing, a multivariable analysis would have been an unnecessary next step anyway, so this study has been included.

For the outcome of complete occlusion of the target vein, the only risk factor associated was compliance with post-procedure compression hosiery ($p<0.05$). No effect sizes were presented. This is not a factor that could be ascertained pre-treatment (although it is conceivable that patients could be asked if they thought they'd be compliant with stockings after treatment) and so has little value in making a pre-treatment prediction about which patients will do well.

For the outcome of any complication, female gender was associated with a greater risk ($p<0.05$). No effect size was reported. For each complication considered separately, female gender was associated with skin staining ($P<0.05$). No effect sizes were given. There were no associations between female gender and any other complications considered singly.

2

G.3 Chapter 7 – assessment for treatment

G.3.1 Diagnostic accuracy of hand held Doppler ultrasound

Table 33: Campbell 1997[44]

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Campbell WB, Niblett PG, Ridler BMF, Peters AS, Thomson JF. Hand held doppler as a screening test in primary varicose veins. British Journal of Surgery 1997; 84: 1541-1543	Diagnostic review study.	85 (122 legs)	Patients referred to the vascular outpatient clinic with primary and previously un-operated varicose veins. **Gender:** 52 women **Age:**range18-89 (median 53).	Hand held doppler. Performed in standing. Tourniquet test used for the GSV. Positioning not given. **>1 second reflux regarded as significant. Carried out by consultant(103 legs), trainee (in 17) and unknown (2 legs).**	Duplex, using a Diasonics VST masters scanner with a 5MHz linear array probe. Positioning not given. **>1 second reflux regarded as significant. Duplex operator not reported**.	**Blinding NOT stated** **Test interval <u>not</u> clear: “another visit”.** **Expertise comparability <u>not</u> clear.** **No previous treatments. CEAP status not reported.**	Sensitivity and specificity	Not reported
Results: Raw data only available for the popliteal fossa (percentages given for the GSV, but not possible to convert these to raw numbers due to lack of data on the numbers with duplex-confirmed reflux).								
popliteal fossa	+ve on duplex	-ve on duplex						
+ve onHHD	28	8						
-ve on HHD	11	74						
Popliteal fossa +ve and –ve predictive values, and all CIs, derived from raw data. No raw data given for groin or 10cm below groin.								
Site examined			**sensitivity**	**Specificity**	**Positive predictive value**		**Negative predictive value**	
Great Saphenous Vein			0.86	0.82	-		-	
10cm below groin (alternative GSV)			0.81	0.85	-		-	
Popliteal fossa			0.72 (0.55-0.85)	0.90(0.82-0.96)	0.78(0.62-0.88)		0.87(0.78-0.93)	

Table 34: Darke 1997[64]

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Darke SG, Vetrivel S, Foy DMA, Smith S, Baker S. A comparison of duplex scanning and continuous wave doppler in the assessment of primary and uncomplicated varicose veins. Eur J Vasc Endovasc Surg 1997; 14: 457-461	Diagnostic accuracy study	73 patients (100 legs)	73 patients referred to a consultant vascular surgeon with primary uncomplicated varicose veins. **Gender:** 55 females; **Age:** mean 47.5 (range 22-74);	continuous wave Doppler, using a Huntleigh dopplex 500 probe at 8MHz. Positioning not given. **Reflux definition not described in terms of duration.** **Carried out by a "single observer".**	Duplex, using an Acuson 128/10 colour duplex scanner with a 7MHz linear array probe. This was carried out blind to the doppler findings. **Reflux defined as >0.5 secs. Carried out by a medical technologist.**	**Blinding carried out** **Test interval not stated** **Expertise comparability <u>not</u> clear.** **Stage of disease and previous treatment history not given.**	Sensitivity and specificity	Not stated
Results: No CIs provided in the paper. The raw data below were gathered from the paper, and the CIs were calculated.								
Great saphenous vein	+ve on duplex	-ve on duplex		**Short saphenous vein**	+ve on duplex	-ve on duplex		
+ve on HHD	83	0		+ve on HHD	19	5		
-ve on HHD	4	13		-ve on HHD	2	74		
In paper only sensitivity and specificity provided, but +ve and –ve predictive values have been calculated from the raw values.								
Site examined	**sensitivity** *[TP/TP+FN]*		**Specificity** *[TN/TN+FP]*		**+ve predictive value** *[TP/TP+FP]*		**-ve predictive value** *[TN/TN+FN]*	

Reference	**Study type**	**No of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
Great saphenous vein	*[83/83+4]* 0.95(0.89-0.99)		*[13/13+0].* 1.00(0.75-1.00)		*[83/83+0]* 1.00(0.95-1.00))		*[13/13+4].* *0.75(0.52-0.89)*	
Short saphenous vein	*[19/19+2]* 0.90(0.70-0.99)		*[74/74+5]* 0.94(0.86-0.98)		*[19/19+5]* 0.79(0.59-0.91)		*[74/74+2]* 0.97(0.91-0.99)	

Table 35: DePalma 1993[76]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
DePalma RG, Hart MT, Zanin L and Massarin EH. Physical examination, doppler ultrasound and colour flow duplex scanning: guides to therapy for primary varicose veins. Phlebology 1993; 8: 7-11.	Diagnostic review study.	40 (80 legs)	Symptomatic patients presenting with primary varicosities in the great saphenous distribution. **Gender:** 31 women; **Age:** 27-64 yrs; All had mild-moderate symptoms. Typical symptoms were aching in the evening. 22/80 limbs had had prior stripping, but were still symptomatic.	Hand held 9.1 MHz CW Doppler pencil probe at an acute angle of 30-45 deg. Patient positioning not described. **No definition of reflux duration threshold**. **Carried out by senior author, who was probably a vascular surgeon, but unclear.**	Duplex, with a QUAD-1 colour flow scanner, with 5MHz probe. Carried out in standing and supine. **No definition of reflux duration threshold. Carried out by 2 vascular technical observers.**	**Blinding carried out** **Test interval not stated** **Expertise comparability not clear.** **28% with prior stripping. CEAP status not reported**	Sensitivity and specificity, positive predictive value, negative predictive value	Not reported
Results: Raw data								
SFJ	+ve on duplex	-ve on duplex		**SFJ in sub-group with previous stripping** n=22		+ve on duplex	-ve on duplex	
+ve onHHD	24	5		+ve onHHD		8	1	
-ve on HHD	26	25		-ve on HHD		9	4	

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
No CIs given in paper. CIs calculated from raw values.								
Site examined	**sensitivity** *[TP/TP+FN]*		**Specificity** *[TN/TN+FP]*		**Positive predictive value** *[TP/TP+FP]*		**Negative predictive value** *[TN/TN+FN]*	
SFJ n=80 limbs	*[24/24+26]* 0.48(0.34-0.63)		*[25/25+5]* 0.83(0.65-0.94)		*[24/24+5]* 0.83(0.66-0.92)		*[25/25+26]* 0.49(0.36-0.62)	
SFJ in sub-group with previous stripping n=22	*[8/8+9]* 0.47(0.26-0.69)		*[4/4+1]* 0.80(0.38-0.96)		*[8/8+1]* 0.89(0.57-0.98)		*[4/4+9]* 0.31(0.13-0.58)	

Table 36: Kent 1998[131]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Kent PJ, Weston MJ. Duplex scanning may be used selectively in patients with primary varicose veins. Ann R Coll Surg Engl 1998;80: 388-393	Diagnostic accuracy study.	72 patients (108 limbs)	People with primary varicose veins, who had not undergone previous injection sclerotherapy or surgical treatment. **Gender:** 20 males and 52 females. **Median age:** 44.5 years (range 19-73 years). **CEAP stage (limbs):** C1: 1/108 C2: 96/108 C3: 0/108 C4: 9/108 C5; 0/108 C6: 2/108	Hand held Doppler, with 8MHz probe (Multi-Duplex). **Carried out by one consultant vascular surgeon.** Measurement performed in the standing position, with the affected limb slightly flexed at hip and knee. The probe placed over the sapheno-femoral junction and the calf compressed. **Reflux lasting longer than 0.5 seconds was regarded as significant**. This was then repeated at the great saphenous vein.	Duplex (with guided pulse wave spectral doppler), using a Siemens Q2000 machine, with a 5 MHz curvilinear probe. Patient measured in standing with weight off the affected limb. **Reversed flow of over 1 second was considered abnormal.** Carried out immediately after hand held Doppler scanning. This was **carried out by another consultant radiologist** who was unaware of the results of the HHD assessment	**Blinding carried out** **Tests followed each other immediately** **Expertise of operators comparable** **No previous treatment and mostly CEAP stage 2**	Sensitivity, specificity. Positive predictive value and negative predictive value of hand held Doppler.	None stated

Results: HHD diagnostic accuracy compared to gold standard of Duplex. **<u>This study did not report the raw data</u>. The data below is all that was presented.**
(* with tourniquet)

Site examined	sensitivity	specificity	Positive predictive value	negative predictive value
SFJ	0.93	0.91	0.96	0.86

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
GSV	0.95	0.68	0.91	0.81				
MTP*	0.87	0.26	0.16	0.92				
SPJ	0.82	0.80	0.44	0.96				
PV*	0.50	0.90	0.44	0.92				

Table 37: Kim 2000[134]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Kim J, Richards S, Kent PJ. Clinical examination of varicose veins – a validation study. Ann Royal College Surgery Engl 2000; 82: 171-175.	Diagnostic accuracy study.	44 patients (70 limbs)	Primary and previously untreated varicose veins presenting for Duplex scanning were tested. Secondary varicose veins and previous surgery patients excluded. **CEAP stages:** C1: 2/70, C2: 67/70 C3: 1/70.	Hand held Doppler with 8MHz probe (Huntleigh technologies). Patient stood on unaffected leg. Probe placed on sapheno-femoral junction. Calf squeezed, and subsequent **reflux of <0.5 sec was deemed significant.** Then repeated over the GSV and SPJ. **Carried out by house officer**	Duplex (with guided pulse wave spectral doppler), using a Diagnostic US systems 3535 machine (B&K Medical, Denmark) machine, with a 5 MHz curvilinear probe. **Reversed flow of over 1 second was considered abnormal.** Carried out immediately after hand held Doppler scanning. **This was carried out by a vascular technologist** who was unaware of the results of the hand held Doppler assessment	**Blinding carried out** **Tests followed each other immediately** **Expertise of operators <u>not</u> comparable.** **No previous treatment and mostly C2**	Sensitivity, specificity. Positive predictive value and negative predictive value of hand held Doppler	None stated

Results: <u>This study did not report the raw data</u>. The data below is all that was presented

Site examined	sensitivity	specificity	Positive predictive value	Negative predictive value
SFJ	0.97	0.73	0.80	0.96
GSV	0.82	0.92	0.84	0.74
SPJ	0.80	0.90	0.57	0.97

Table 38: Mercer 1998[167]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Mercer KG, Scott DJA, Berridge DC. Pre-operative duplex imaging is required before all operations for primary varicose veins. British journal of Surgery 1998; 85: 1495-1497.	Diagnostic accuracy study.	61 patients (81 legs)	Primary varicose veins.	Hand held doppler, with 8MHz probe (Multi-Dopplex). **Carried out by one consultant vascular surgeon.** In standing with the affected leg slightly flexed, reflux looked for at sapheno-femoral junction, great saphenous vein and sapheno-popliteal junction. **Reflux >0.5 sec regarded as significant.**	At a separate appointment (time after not described) Colour flow duplex using a Siemens Quantum 2000 or B&K 3535 (with Acuson 128 5MHz curvilinear probe). Positioning unclear. **Carried out by a consultant vascular radiologist. Reflux >0.5 sec regarded as significant.**	**Blinding definitely NOT carried out (duplex operator reported as having access to hand held Doppler results)** **Test interval unclear, but described as at a separate appointment** **Expertise of operators comparable.** **Treatment history and stage of disease unclear**	Sensitivity, specificity of hand held Doppler	Not reported
Results: Raw results:								
SFJ	+ve on duplex	-ve on duplex			**SPJ**	+ve on duplex	-ve on duplex	
+ve onHHD	43	2			+ve onHHD	20	4	
-ve on HHD	16	28			-ve on HHD	6	59	
Thigh Perforators	+ve on duplex	-ve on duplex						
+ve onHHD	18	8						
-ve on HHD	17	46						

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Positive and negative predictive values not given in paper, but calculated from raw values.								
Site examined	**sensitivity** *[TP/TP+FN]*		**Specificity** *[TN/TN+FP]*		**Positive predictive value** *[TP/TP+FP]*		**Negative predictive value** *[TN/TN+FN]*	
SFJ	*[43/43+16]* 0.73 (0.60-0.84)		*[28/28+2]* 0.93 (0.78-0.99)		*[43/43+2]* 0.96 (0.85-0.99)		*[28/28+16]* 0.64 (0.50-0.76)	
SPJ	*[20/20+6]* 0.77 (0.56-0.91)		*[59/59+4]* 0.94 (0.85-0.98)		*[20/20+4]* 0.83 (0.64-0.93)		*[59/59+6]* 0.91 (0.81-0.96)	
Thigh perforator	*[18/18+17]* 0.51 (0.34-0.69)		*[46/46+8]* 0.85 (0.73-0.93)		*[18/18+8]* 0.69 (0.5-0.84)		*[46/46+17]* 0.73 (0.61-0.82)	

1 **Table 39: Rautio 2002B[226]**

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
Rautio T, Perala J, Eiik H, Haukipuro K, Juvonen T. Influence of preoperative duplex ultrasonography on the operative procedure for primary varicose vein surgery. Phlebology 2002; 16: 149-153	Diagnostic accuracy study.	49 patients (62 legs).	Patients with primary, previously untreated and uncomplicated varicose veins, referred for surgery. **Exclusion:** previous history of DVT. **Median age:** 45.5 years (range 19-66). **Gender:** 5 male and 44 female patients. Venous disability score was 0-1 in all cases. Superficial reflux was detected in 55/62 limbs. No deep vein/perforator reflux detected.	Hand held Doppler with an 8MHz probe (Hadeco minidoppler ES-100X). Patients tested in a semi-supine position. The sapheno-femoral junction, and the great saphenous vein at three separate points, were insonated. **An audible flow signal lasting for > 1 sec was significant**. The Sapheno-popliteal junction and short saphenous vein were also insonated if there were clinical evidence suggesting involvement. **Done by an experienced General Surgeon.**	Duplex scanning with a 5MHz probe (Toshiba Power Vision 8000, Japan). Patients supine with slight truncal elevation. **Reverse flow of >1 second regarded as pathological**. **Done by a consultant vascular radiologist** blinded to the hand held Doppler results.	**Blinding carried out** **Tests followed each other at same appointment** **Expertise of operators comparable.** **No previous treatment and venous disability score of 0-1**	Sensitivity, specificity. Positive predictive value and negative predictive value of hand held Doppler.	None stated

Results: Raw data:

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
SFJ	+ve on duplex	-ve on duplex			**GSV1 (mid thigh) [these findings were used for the report]**	+ve on duplex	-ve on duplex	
+ve onHHD	31	1			+ve onHHD	24	1	
-ve on HHD	17	13			-ve on HHD	25	12	
GSV2 (popliteal fossa)	+ve on duplex	-ve on duplex			**GSV3 (calf)**	+ve on duplex	-ve on duplex	
+ve onHHD	22	3			+ve onHHD	15	3	
-ve on HHD	19	18			-ve on HHD	17	27	
95% CIs are also included in round brackets. *Raw data in italics and square brackets*.								
Site examined	**sensitivity** *[TP/TP+FN]*		**Specificity** *[TN/TN+FP]*		**+ve predictive value** *[TP/TP+FP]*		**-ve predictive value** *[TN/TN+FN]*	
SFJ	[31/31+17] 0.65 (0.49-0.78)		[13/13+1] 0.93 (0.66-1.00)		[31/31+1] 0.97 (0.84-0.99)		[13/13+17] 0.45 (0.29-0.62)	
GSV1 (mid thigh)	[24/24+25] 0.49 (0.34-0.64)		[12/12+1] 0.92 (0.64-1)		[24/24+1] 0.96 (0.81-0.99)		[12/12+25] 0.32 (0.20-0.49)	
GSV2 (popliteal fossa)	[22/22+19] 0.54 (0.39-0.68)		[18/18+3] 0.86 (0.65-0.95)		[22/22+3] 0.88 (0.70-0.96)		[18/18+19] 0.47 (0.33-0.64)	
GSV3 (calf)	[15/15+17] 0.47 (0.30-0.64)		[27/27+3] 0.90 (0.74-0.97)		[15/15+3] 0.83 (0.61-0.94)		[27/27+17] 0.61 (0.47-0.74)	

Table 40: Rautio 2002A[225]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Rautio T, Perala J, Biancari F, Wiik H, Ohtonen P, Haukipuro K, Juvonen T. Accuracy of hand held doppler in planning the operation for primary varicose veins. Eur J Vasc Endovasc Surg 2002; 24: 450-455	Diagnostic review study. Handheld Doppler and Duplex done on the same day by different people.	111 patients (142 limbs)	Patients referred for surgical treatment of varicose veins with primary, uncomplicated and previously untreated varicose veins **Exclusion:** History of lower limb venous thrombosis **Gender:** 96 females **Mean age** (range): 42(23-76) **mean BMI** (range): 25.6(18.3-52.8); **Venous disability score** 0: 14/111, 1: 85/111, 2: 12/111; **CEAP stage:** C1 (5/142), C2 (67/142), C3 (59/142), C4 (11/142).	Hand held doppler using a 8MHz probe (Hadeco mini-doppler ES-100X). Patients were examined in a semi-supine position with the upper body elevated at 45 degrees. **Audible flow signal of >1 sec was taken as the threshold of significant reflux**. **Carried out by consultant general surgeon.**	Duplex scanning with a 7.5MHz probe (Toshiba Power Vision 8000). Positioning as for the hand held Doppler examination. **Reflux >1 second was regarded as significant**. **Carried out by consultant vascular radiologist.**	**Blinding carried out** **Test interval within the same day** **Expertise of operators comparable** **Mostly C2-3, and had no previous treatments.**	Sensitivity and specificity, positive predictive value, negative predictive value and kappa co-efficient.	Not reported.
Results:								
SFJ	+ve on duplex	-ve on duplex		**GSV1 (upper thigh)**	+ve on duplex	-ve on duplex		
+ve onHHD	59	1		+ve onHHD	54	8		
-ve on HHD	46	36		-ve on HHD	39	41		

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
GSV2 (lower thigh)	+ve on duplex	-ve on duplex		**GSV3 (calf)**	+ve on duplex	-ve on duplex		
+ve onHHD	53	10		+ve onHHD	46	14		
-ve on HHD	33	59		-ve on HHD	23	59		
SPJ	+ve on duplex	-ve on duplex						
+ve onHHD	3	4						
-ve on HHD	10	95						
95% CIs are also included in round brackets. *Raw data in italics and square brackets*.								
Site examined	**sensitivity** *[TP/TP+FN]*	**Specificity** *[TN/TN+FP]*	**+ve predictive value** *[TP/TP+FP]*		**-ve predictive value** *[TN/TN+FN]*		**kappa co-efficient**	
SFJ n=142	*[59/59+46]* 0.56(0.46-0.66)	*[36/36+1]* 0.97(0.86-100)	*[59/59+1]* 0.98(0.91-1)		*[36/36+46]* 0.44(0.34-0 .55)		38(24-53)	
GSV1 (upper thigh) n=142	*[54/54+39]* 0.58(0.47-0.68)	*[41/41+8]* 0.84(0.70-0.93)	*[54/54+8]*0.87(0.77-0.93)		*[41/41+39]* 0.51(0.41-0.62)		36(21-51)	
GSV2 (lower thigh) n=142	*[53/53+33]* 0.62(0.51-0.71)	*[59/59+10]* 0.82(0.70-0.90)	*[53/53+10]*0.84(0.73-0.91)		*[59/59+33]* 0.58(0.47-0.69)		41(26-56)	
GSV3 (calf) n=142	*[46/46+23]* 0.67(0.55-0.77)	*[59/59+14]* 0.81(0.70-0.88)	*[46/46+14]*0.77(0.65-0.86)		*[59/59+23]* 0.72(0.61-0.81)		48(33-62)	
SPJ n=112	*[3/3+10]* 0.23(0.05-0.54)	*[95/95+4]* 0.96(0.90-0.99)	*[3/3+4]*0.43(0.16-0.75)		*[95/95+10]* 0.91(0.83-0.95)		24(-14–61)	

Table 41: Salaman 1995[236]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Salaman RA, Fligelstone LJ, Wright N, Pugh KG, Harding KG, Lane IF. Hand held bi-directional doppler versus colour duplex scanning in the pre-operative assessment of varicose veins. J Vasc Invest 1995; 1:183-6	Diagnostic accuracy study	42(72)	Patients awaiting varicose vein surgery or attending the vascular outpatient clinic with symptomatic varicose veins.	Hand held Doppler with a Dopplex MD2 bi-directional hand-held Doppler unit with an 8MHz probe. **Reflux duration threshold not stated. Done by an experienced vascular research fellow.**	Duplex done with a Toshiba SPA270A scanner with a 5MHz linear array probe. **Done by a vascular medical scientist. Reflux defined as >0.5 secs of retrograde flow.**	**Blinding unclear – reported that "both investigations were reported independently"** **Test interval not reported.** **Expertise of operators probable.** **Surgical history unclear and disease severity unclear.**	Sensitivity and specificity, Positive predictive value, Negative predictive value	Not stated
Results: NB: these data are extracted from data provided, in a different form, in the paper. Note how the total n in each grid varies, from 72 (the expected value) to 77. This must be due to errors in the data on the paper.								
SFJ	+ve on duplex	-ve on duplex		**SPJ**	+ve on duplex	-ve on duplex		
+ve onHHD	49	1		+ve onHHD	10	6		
-ve on HHD	4	18		-ve on HHD	8	50		
Thigh perforator	+ve on duplex	-ve on duplex		**calf/ankle perforator**	+ve on duplex	-ve on duplex		
+ve onHHD	2	13		+ve onHHD	2	4		
-ve on HHD	5	54		-ve on HHD	4	67		

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
common femoral	+ve on duplex	-ve on duplex		**popliteal**	+ve on duplex	-ve on duplex		
+ve onHHD	0	13		+ve onHHD	2	1		
-ve on HHD	1	58		-ve on HHD	3	68		
Site examined	**sensitivity** *[TP/TP+FN]*		**specificity** *[TN/TN+FP]*		**Positive predictive value** *[TP/TP+FP]*		**Negative predictive value** *[TN/TN+FN]*	
SFJ	[49/49+4] 0.92(0.82-0.98)		[18/18+1] 0.95(0.74-1.00)		[49/49+1] 0.98(0.90-0.99)		[18/18+4] 0.82(0.62-0.93)	
SPJ	*[10/10+8]* 0.56(0.31-0.78)		*[50/50+6]*0.89(0.78-0.96)		*[10/10+6]* 0.63(0.39-0.82)		*[50/50+8]* 0.86(0.75-0.93)	
Thigh perforators	*[2/2+5]* 0.29(0.04-0.71)		*[54/54+13]* 0.81(0.69-0.89)		*[2/2+13]* 0.13(0.04-0.38)		*[54/54+5]* 0.92(0.82-0.96)	
Calf/ankle perforators	*[2/2+4]* 0.33(0.10-0.70)		*[67/67+4]* 0.94(0.86-0.98)		*[2/2+4]* 0.33(0.10-0.70)		*[67/67+4]* 0.94(0.86-0.98)	
Popliteal	*[2/2+3]* 0.4(0.05-0.85)		*[68/68+1]* 0.99(0.92-1)		*[2/2+1]* 0.67(0.21-0.94)		*[68/68+3]*0.96(0.88-0.99)	

1 **Table 42: Schultheiss 1997**[241]

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
Schultheiss R, Billeter M, Bollinger A, Franzeck UK. Comparison between clinical examination, cw-Doppler Ultrasound and Colour-duplex sonography in the diagnosis of incompetent perforating veins. Eur J vasc Endovasc surg 1997; 13: 122-126.	Diagnostic accuracy study.	19 patients (19 limbs)	Patients with chronic venous insufficiency. 2 described as C3, 14 as C4 and 3 as C5. **Exclusion:** C6 disease, PAD, cardiac problems, diabetes mellitus, nephropathy. **Age:** Mean age of the women was 62.8 years (range 44-79 years) and of the men was 56.3 years (range 32-76).	Hand held cw doppler ultrasound **carried out by experienced medical doctor.** 8.2 or 5.3 MHz pencil probe (Parks Electronics Lab model 10110). Testing carried out in standing over areas of marked fascial defect. **No definition of reflux given in terms of duration.**	Duplex **carried out by another medical doctor** blinded to HHD results. Linear 5 and 7 MHz probes were used (Acuson 128 XP/10). Done in standing. **Reflux defined as reverse flow of >0.5 sec.**	**Blinding carried out** **Test interval not stated** **Expertise comparability <u>not</u> clear.** **Mostly C4. Previous treatment status not given.**	Sensitivity, specificity of hand held Doppler.	Swiss Phlebology Society.
RESULTS: **<u>Usable raw data was not presented.</u>** **Only the results below were mentioned in the discussion**								
Site examined		**sensitivity**	**specificity**					
perforating veins		0.29	0.15					

2

Table 43: van der Heijden 1993[276]

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
van der Heijden FHWM, Bruyninckx CMA. Preoperative colour-coded duplex scanning in varicose veins of the lower extremity. Eur J Surg 1993; 159: 329-333	Diagnostic study	48 (68 legs)	Patients with leg varicose veins. **Gender:** 35 women; **Age:** mean age 48 years (range 16-77); **Previous treatment:** 10 had had previous stripping.	Continuous wave doppler done by a vascular technician. No other details given of positioning or definition of reflux in terms of duration.	Duplex carried out by a surgical resident. Toshiba SSA-270A machine used, with 5MHz linear array transducer. **Patients examined upright. Reflux of 0.5 seconds regarded as significant.**	**Blinding carried out** **Test interval <u>not</u> stated, but appears to be same day** **Expertise comparability probable.** **21% with prior stripping. CEAP status not reported**	No diagnostic outcomes presented by the paper, but some raw data allowed calculations.	None stated
Results: These were based on interpretation of the data in the paper which was presented (the numbers with duplex signs of incompetence were given, and also specific information given where there was discordance between HHD and duplex)**. In some cases a false negative result was not due to failure to observe reflux, but an incorrect identification of the source of reflux**. Accuracy of these data is suspect.								
SFJ	**+ve on duplex**	**-ve on duplex**		**Great saphenous vein**	**+ve on duplex**	**-ve on duplex**		
+ve onHHD	45	1		+ve onHHD	41	1		
-ve on HHD	2	20		-ve on HHD	4	22		
short saphenous vein	**+ve on duplex**	**-ve on duplex**		**Perforating veins**	**+ve on duplex**	**-ve on duplex**		
+ve on HHD	16	0		+ve on HHD	10	1		
-ve on HHD	2	50		-ve on HHD	9	17		

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Other issues of importance**	**Outcome measures**	**Source of funding**
SPJ	**+ve on duplex**	**-ve on duplex**						
+ve on HHD	17	0						
-ve on HHD	0	51						
Site examined	**sensitivity** *[TP/TP+FN]*		**Specificity** *[TN/TN+FP]*		**Positive predictive value** *[TP/TP+FP]*		**Negative predictive value** *[TN/TN+FN]*	
SFJ	*[45/45+2]* 0.96(0.85-0.99)		*[20/20+1]* 0.95(0.76-1)		*[45/45+1]* 0.98(0.89-0.99)		*[20/20+2]* 0.91(0.72-0.98)	
Great saphenous vein	*[41/41+4]* 0.91(0.79-0.98)		*[22/22+1]* 0.96(0.78-1)		*[41/41+1]* 0.98(0.88-0.99)		*[22/22+4]* 0.84(0.67-0.94)	
Short saphenous vein	*[16/16+2]* 0.89(0.65-0.99)		*[50/50+0]* 1(0.93-1)		*[16/16+0]* 1(0.77-1)		*[50/50+2]* 0.95(0.86-0.99)	
Perforating veins	*[10/10+9]* 0.53(0.29-0.76)		*[17/17+1]* 0.94(0.73-1)		*[10/10+1]* 0.91(0.62-0.98)		*[17/17+9]* 0.65(0.46-0.81)	
SPJ	*[17/17+0]* 1(0.8-199)		*[51/51+0]* 1(0.93-1)		*[17/17+0]* 1(0.78-1)		*[51/51+0]* 1(0.91-1)	

Table 44: Wills 1998[284]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
Wills V, Moylan D, Chambers J. The use of routine duplex scanning in the assessment of varicose veins. Aust NZ J Surg 1998; 68: 41-44	Diagnostic accuracy study	188 patients (315 legs)	Patients with varicose veins who had been referred to a vascular surgeon. **Gender:** 142 female **Mean age** 54.1 yrs (range 21-79 years) **Previous treatment:**122/315 legs Of these, 86 legs had had high ligation ± other treatment, 8 had stab avulsions and 29 had sclerotherapy. 16/315 legs were thought to have secondary varicose veins (15 previous DVT and 1 arteriovenous malformation); skin changes present in 99/315 legs C4: 69 C6: 30 No disease, or only	Hand held doppler combined with clinical assessment. Parks hand-held doppler probe (8MHz) used. This was combined with clinical assessment, involving trendelenburg testing with a tourniquet. Patient position not described. **Reflux definition not described in terms of duration. Done by a specialist vascular surgeon.**	Duplex, using a Toshiba 270 scanner with a 5 MHz probe and colour flow imaging. Leg being examined was in a dependent position. **Reflux defined as retrograde flow of >1 sec** after the release of manual calf compression. **Done by a trained vascular technician.**	**Blinding NOT stated.** **Time interval not stated. Delay likely as stated that patient were 'referred' for duplex.** **Expertise of operators probably comparable.** **39% had had previous treatment and 31% had skin changes**	Sensitivity and specificity	None reported

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Other issues of importance	Outcome measures	Source of funding
			superficial tributaries, with a normal great saphenous vein, was seen in 35 legs.					
Results: <u>Insufficient raw data given.</u> The data below is all that was given in the paper.								
Site examined			**Sensitivity**	**Specificity**				
Sapheno-femoral junction			71.2%	70.9%				
Sapheno-popliteal junction			36.1%	92.1%				
Perforating veins			43.6%	78.7%				
Deep Venous			29.2%	94.8%				
SFJ of a sub-group of legs with 'uncomplicated' varicose veins (no skin changes and not recurrent)			80.2%	52.2%				

G.3.2 Duplex assessment prior to interventional treatment

Table 45: Blomgren 2006A[25]

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Blomgren L, Johansson G, Bergqvist D. Quality of life after surgery for varicose veins and the impact of pre-operative duplex; reflux based on a randomised trial. Annals of vascular surgery 2006; 20: 30-34. (NB – Same study as Blomgren 2011[26] and Blomgren 2005[24])	RCT. Sealed envelope system used for allocation concealment. No mention of how the randomised sequence was drawn up. Study involved 20 surgeons.	293 randomised (though unclear). 237 reported to have given full follow-up data. 250 patients attended 2 year follow-up. Unclear how many legs were involved in the study. No reports of any who did not complete treatment.	**Inclusion:** Primary varicose veins. **Exclusion:** pure cosmetic complaints, previous venous surgery or sclerotherapy, history of suspected or manifest deep venous thrombosis, active or healed leg ulcer, peripheral arterial disease, previous significant trauma to the leg, general illness and drug or alcohol abuse. **Baseline characteristics**: Poorly described (but available in Blomgren 2005). Overall mean (range) age was 47 (22-73) and 71% were women. 45 with bilateral surgery, 16 in duplex group and 29 in no duplex group (p=0.030. Skin changes present in 18%, with no differences between the groups. An important confounder was the surgery used, as this differed between groups. The duplex group had more patients than the non-duplex group with removal of the GSV and SSV, and less patients in the duplex group than the non-duplex group had avulsions.	Pre-operative Duplex scan. Surgical procedures that followed were removal of GSV/SSV, extrafascial ligation of perforators, and stab avulsions of tributaries.	No pre-operative duplex scan. Surgical procedures that followed were removal of GSV/SSV, extrafascial ligation of perforators, and stab avulsions of tributaries.	2 years	Quality of life Patient assessed symptoms Rates of recurrence and reoperation (dealt with in detail in Blomgren 2005)	None

Results:

	Duplex	**No duplex**

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

patient assessed symptoms operated limbs unchanged or worse at 2 years compared to baseline	15/130	19/120
Rates of recurrence and reoperation	significantly higher in no duplex group (more details given in Blomgren 2005)	
Quality of life – SF-36 domains	No significant difference between the groups for any SF-36 domain at 1 or 2 years. The results were the same when patients with bilateral and unilateral varicose veins surgery were analysed separately. No data given for each group.	

Table 46: Blomgren 2005[24]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Blomgren L, Johansson G, Bergqvist D. Randomised clinical trial of routine preoperative duplex imaging before varicose vein surgery. British Journal of Surgery 2005; 92: 688-694
(NB – Same study as Blomgren 2011 and Blomgren 2006)</td>
<td>RCT. Sealed envelope system used for allocation concealment. If both legs included, both given the same randomisation (i.e. randomised by patient).
No mention of how the randomised sequence was drawn up.
Study involved 20 surgeons.</td>
<td>308 randomised but 15 initially excluded because of refusal, pregnancy and remote residency. In the duplex group 8 (8 legs) were excluded (2 patient request, 2 inclusion criteria violation, 2 moved to remote region, 2 pregnancy). In the no duplex group; 7 (7 legs) were excluded (4 patient request, 2 inclusion criteria violation, 1 moved to remote region). This left, by the point of the duplex intervention, 148 patients (166 legs) in the duplex group and 145 patients (177 legs) in the no duplex</td>
<td>Inclusion: Primary varicose veins, with an indication for surgery (in the view of the surgeon).
Exclusion: pure cosmetic complaints, previous venous surgery or sclerotherapy, history of suspected or manifest deep venous thrombosis, active or healed leg ulcer, peripheral arterial disease, previous significant trauma to the leg, general illness and drug or alcohol abuse.
Baseline characteristics:
<table>
<tr><th></th><th>Duplex</th><th>no duplex</th></tr>
<tr><td>legs</td><td>166</td><td>177</td></tr>
<tr><td>M:F</td><td>44:122</td><td>43:134</td></tr>
<tr><td>age</td><td>47.9(11.1)</td><td>44.6(12.4)</td></tr>
<tr><td>CEAP >C3</td><td>29/166</td><td>22/177</td></tr>
<tr><td>GSV stripping</td><td>125/166</td><td>83/177</td></tr>
<tr><td>SSV removal</td><td>8/166</td><td>4/177</td></tr>
<tr><td>GSV + SSV removal</td><td>0/166</td><td>1/177</td></tr>
<tr><td>local phlebectomies done</td><td>33/166</td><td>89/177</td></tr>
</table></td>
<td>Pre-operative Duplex scan, using a colour flow duplex machine (Acuson XP128 and Acuson Sequioa 512). Reflux with a duration of >0.5 seconds was regarded as significant. (Some surgeons also did a pre-operative hand held Doppler scan).
Surgical procedures that followed were removal of GSV/SSV, extrafascial</td>
<td>No pre-operative duplex scan. (But some surgeons did a pre-operative hand held Doppler scan).
Surgical procedures that followed were removal of GSV/SSV, extrafascial ligation of perforators, and stab avulsions of tributaries. Most done under general</td>
<td>2 years</td>
<td>Reflux at 2 months
Reflux at 2 years</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		group. Loss to follow-up; **2 months:** Duplex – 5 people (6 legs); No duplex – 8 people (11 legs). **2 years:** Duplex – 35 people (39 legs); No duplex – 39 people (48 legs).		ligation of perforators, and stab avulsions of tributaries. Most done under general anaesthetic. Importantly, in the duplex group the duplex assessment led to the alteration of surgery from the pre-determined course in 44/166 legs.	anaesthetic. Naturally, in the absence of duplex assessment, the predetermined course based on clinical examination was adhered to.			

Results: Analysis was done by legs. For reflux, intention to treat results given unless stated.

	Duplex	No duplex
SFJ reflux at 2 months	10/160	37/166
SPJ reflux at 2 months	4/160	9/166
SFJ and/or SPJ reflux (i.e. reflux anywhere!) at 2 months	14/160	44/166
SFJ reflux at 2 years	14/127	44/129

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SPJ reflux at 2 years				7/127	13/129			
SFJ and/or SPJ reflux (i.e. reflux anywhere!) at 2 years				19/127	53/129			
Need for further operation in first 2 years (indication was persistent or recurrent symptoms, or patients' wish)				3/145 (including patient with phlebectomies at another hospital)	14/147			
Adverse events								
DVT at 2 years				0/145	0/147			
Proportion with improvement in CEAP category at 2 years				104/145	86/147			
Proportion with skin changes (C4+) at 2 years (baseline difference, but more in group 1 at baseline, so does not affect validity of result on right)				15/145	19/147			
Proportion with oedema (C3) at 2 years (baseline difference, with more in group 2 at baseline, which threatens the validity of the result on right)				25/145	38/147			

Table 47: Blomgren 2011[26]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Blomgren L, Johansson G, Emanuelsson L, Dahlberg-Akerman, Thermaenius P, Bergqvist D. Late follow-up of a randomised trial of routine duplex imaging before varicose vein surgery. British Journal of surgery 2011; 98: 1112-1116.(NB – Same study as Blomgren 2005 and Blomgren 2006)</td>
<td>RCT. Sealed envelope system used for allocation concealment. If both legs included, both given the same randomisation (i.e. randomised by patient).
No mention of how the randomised sequence was drawn up.
Study involved 20 surgeons.</td>
<td>308 randomised but 15 initially excluded because of refusal, pregnancy and remote residency. In the duplex group 8 (8 legs) were excluded (2 patient request, 2 inclusion criteria violation, 2 moved to remote region, 2 pregnancy). In the no duplex group 7 (7 legs) were excluded (4 patient request, 2 inclusion criteria violation, 1 moved to remote region). This left, by the point of the duplex intervention, 148 patients (166 legs) in the duplex group and 145 patients (177 legs) in the no duplex group.
Loss to follow-up;
2 months: Duplex – 5 people (6 legs); No</td>
<td>Inclusion: Primary varicose veins, with an indication for surgery (in the view of the surgeon).
Exclusion: pure cosmetic complaints, previous venous surgery or sclerotherapy, history of suspected or manifest deep venous thrombosis, active or healed leg ulcer, peripheral arterial disease, previous significant trauma to the leg, general illness and drug or alcohol abuse.
Baseline characteristics:
<table>
<tr><th></th><th>Duplex</th><th>no duplex</th></tr>
<tr><td>legs</td><td>166</td><td>177</td></tr>
<tr><td>M:F</td><td>44:122</td><td>43:134</td></tr>
<tr><td>age</td><td>47.9(11.1)</td><td>44.6(12.4)</td></tr>
<tr><td>CEAP >3</td><td>29/166</td><td>22/177</td></tr>
<tr><td>GSV stripping</td><td>125/166</td><td>83/177</td></tr>
<tr><td>SSV removal</td><td>8/166</td><td>4/177</td></tr>
<tr><td>GSV + SSV removal</td><td>0/166</td><td>1/177</td></tr>
<tr><td>local phlebectomies done</td><td>33/166</td><td>89/177</td></tr>
</table>
</td>
<td>Pre-operative Duplex scan, using a colour flow duplex machine (Acuson XP128 and Acuson Sequioa 512). Reflux with a duration of >0.5 seconds was regarded as significant. (Some surgeons also did a pre-operative HHD scan).
Surgical procedures that followed</td>
<td>No pre-operative duplex scan. (But some surgeons did a pre-operative HHD scan).
Surgical procedures that followed were removal of GSV/SSV, extrafascial ligation of perforators, and stab avulsions of tributaries. Most done under general anaesthetic. Naturally, in the absence of duplex</td>
<td>7 years</td>
<td>Reflux at 7 years</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		duplex – 8 people (11 legs). **2 years:** Duplex – 35 people (39 legs); No duplex – 39 people (48 legs). **7 years:** Clinical examination: Duplex: 62 people (70 legs); No duplex: 56(88). Interview and info from patient notes: Duplex: 34 people (42 legs); No duplex: 32(43).		were removal of GSV/SSV, extrafascial ligation of perforators, and stab avulsions of tributaries. Most done under general anaesthetic. Importantly, in the duplex group the duplex assessment led to the alteration of surgery from the pre-determined course in 44/166 legs.	assessment, the predetermined course based on clinical examination was adhered to.			

Results:

	Duplex	No Duplex
SFJ reflux at 7 years	11/95	38/99
SPJ reflux at 7 years	2/95	9/99

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SFJ and/or SPJ reflux (i.e. reflux anywhere!) at 7 years				13/95	46/99			
Condition of treated leg compared to before surgery (Unchanged or worse) at 7 years				16/123	28/108			
Quality of life – SF-36 at 7 years				No data given, apart from statement that there were no differences in any SF-36 variable between groups (reporting bias).				
Reoperation or scheduled for reoperation at 7 years				15/124	38/134			
Complications of varicose veins at 7 years								
Venous ulcer				0/70	0/88			
Hyper-pigmentation or eczema				3/70	9/88			

1

Table 48: Smith 2002[251]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Smith JJ, Brown L, Greenhalgh RM, Davies AH. Randomised trial of pre-operative colour duplex marking in primary varicose vein surgery: outcome is not improved. Eur j Vasc Endovasc Surg 2002; 23: 336-343.	RCT. Randomisation done with sealed envelope system with allocation by a third party. Randomised by patient not leg.	149 patients randomised. None lost to follow-up and none discontinued intervention.	**Inclusion:** patients with primary varicose veins without venous ulceration. **Baseline characteristics:** No details on demographic characteristics. However, clear information on the surgery each group received. The groups were very similar for the number of “HSL/strip/phlebectomy” procedures, and “phlebectomy alone” procedures, but the duplex group had more SPJ and phlebectomies, and more “short and long saphenous system together” procedures. However the latter two classes only comprised a very small proportion of all procedures and so broadly the surgical procedures were comparable. Quality of life was described as comparable for all quality of life measures.	Pre-surgical duplex assessment. Duplex carried out by an experienced vascular technologist. Accuson 2000 scanner with 7.5 MHz linear array probe was used. Hand held HD assessment also carried out, using an Imax continuous wave doppler with 8MHz probe. **Common procedures:** operative procedures were done with general anaesthetic. For long saphenous system, flush sapheno-femoral transfixion with division of surrounding branches and removal of the great saphenous vein was carried out. For small saphenous vein system, flush sapheno-popliteal transfixion and removal of the small saphenous vein was carried out.	No pre-surgical duplex assessment. Unclear, but it is likely these patients *did* have hand held Doppler assessment. N=97	12 months	Quality of life Reflux	None stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Tributary varicosities removed with phlebectomy hooks or mosquito clips. N=92				

Results:

	Duplex	No Duplex
Reflux SFJ 6weeks	1/92	1/97
Reflux GSV 12 months	8/92	9/97*
Reflux SSV 6 weeks	4/92	6/97
Reflux SSV 12 months	6/92	8/97
Reflux perforators 6 weeks	1/92	5/97
Reflux perforators 12 months	4/92	15/97
Development of new branch varicosities at 12 months	8/92	9/97
Aberdeen Questionnaire (AVVQ) at 6 weeks (NO VARIANCE GIVEN)	10.85	15.85 (P=0.034)
Aberdeen Questionnaire (AVVQ) at 12 months	No difference reported [p=0.187] (data in low resolution figure, no data in text)	
SF 36 6 weeks	No diff reported p>0.38 (all domains)	
SF 36 12 months	No diff reported p>0.15 (all domains)	

* paper reports a total of 17 having GSV at 12 months, and then “of which 8 were in the duplex group and 19 in the no duplex group”. This was assumed to be a typographical error, and that it should have been 9 rather than 19.

G.4 Chapter 8 – conservative management

G.4.1 Compression vs. no treatment

Table 49: Anderson 1990[7]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Anderson JH, Geraghty JG, Wilson YT, Murray GD, McArdle CS, Anderson JR. Paroven and graduated compression hosiery for superficial venous insufficiency. 1990; 5: 271-276.	Randomised cross-over trial. Four groups were involved – Paroven alone; hosiery and placebo; paroven and hosiery; and placebo alone. The subjects were randomised to start in one of these 4 groups, and treatment sequences were balanced within groups of 12 in three Latin squares. **Only the results from placebo alone and hosiery and placebo are included in this evidence table.** No wash-out	72. 6 did not complete the trial. Not possible to determine the numbers for each treatment group. No ITT reported.	Mean age 40 years (range 20-61 years). 39 patients spent at least 2/3 of their time at work standing. **Inclusion:** patients on waiting list for varicose veins surgery (mean of 6 months on list) who indicated the presence of at least 2 of the following symptoms: leg pain, heaviness, itch, cramps, swelling. **Exclusion:** If the only complaint was cosmetic distress. Age >65 years; clinical evidence of peripheral arterial disease (PAD), concurrent treatment with diuretics, Ca^{2+} antagonists, NSAIDs, vasodilators, or corticosteroids; history of DVT. **Baseline characteristics:** Not given for the 4 randomised cross-over groups.	Full length hosiery fitted to give a pressure at the ankle of 30-40 mmHg. Hosiery removed in bed. Used for 4 weeks	Placebo is not described. It is likely it was a sham pill, but unclear.	Length of each treatment – 4 weeks.	Patient assessed symptoms: (using visual analogue scale (VAS).	not stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	periods described – but patients were supposed to attend for post-test outcome assessment after 50 days, so this implies a wash-out of 22 days. Details of randomisation and allocation concealment not given. No evidence of blinding.							

Results: VAS scores at the end of the 4 week treatment period are given. The risk of bias from order effects (carry-over) minimised by Latin squares method of ensuring balanced ordering of treatments.

VAS (higher the worse the severity)	**Compression [mean(SE)]**	**Placebo [mean(SE)]**	**p value (post-hoc)**
Pain	34.7 (3.6)	37.6 (3.6)	0.06
heaviness	34.1(3.8)	36.3 (3.5)	0.39
itch	32.0 (3.8)	30.5 (3.9)	0.56
swelling	28.2 (3.6)	35.3 (3.7)	0.13
night cramps	22.4(3.1)	24.9 (3.0)	0.24
body image concerns	43.2(4.6)	41.1 (4.7)	0.43

Author's conclusions: No conclusions made for hosiery alone.

Table 50: Benigni 2003[19]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Benigni JP, Sadoun S, Allaert FA, Vin F. Efficacy of Class 1 elastic compression stockings in the early stages of chronic venous disease. International Angiology 2003; 22: 383-392	RCT. Multi-centre cross-over trial, with 7 day washout period. Randomised, but method not mentioned. No allocation concealment mentioned. Double blinded, but few details given. Withdrawal: 8 by day 14, further 3 by day 21 and further 3 by day 35 (total=14). Ignoring losses in the wash-out period the placebo group lost 7 over the two periods, but the intervention group lost only 4. **NB: For all outcomes (except mood and daily work activity) the detailed results given in the paper are ONLY from the first phase, PRIOR to cross-over. Hence this is not truly a cross-over study. Full cross-over results were given for mood and daily work activity but no reasons**	125. ITT analysis used. Used on those patients who had worn “study stockings at least once” and who had been evaluated at least once.	**Inclusion:** female patients aged 18-75 years, with early stage Chronic Venous Disease (CVD) of the legs. Thread veins, non-saphenous varicose veins (<3mm) or ankle oedema without skin changes. Symptoms including pain, heavy legs, cramps, paraesthesia or ankle swelling. Global painful leg discomfort lasting >8 days, and with a visual analogue scale (VAS) of 4/10 or more on the day of testing. Competent deep venous trunks, competent greater saphenous veins (<5mm), competent lesser saphenous veins (<4mm), competent calf perforating veins, shown by a venous refilling time of >24 seconds and an ankle diameter of 20-26cm and a maximum calf diameter of 33-43cm. **Exclusion:** male patients, suffering from chronic or severe disease. Symptoms of signs in the legs due to pathology of cardiac, renal, hepatic, metabolic, neurological, osteo-articular or traumatic origin. BMI>30. Any risk factors for worsening CVD: recent venous thrombosis, pregnancy or childbirth within 6 months. Past history of DVT. Skin changes, permanent ankle oedema. Ultrasound evidence of valvular incompetence in the sapheno-femoral or sapheno-	Class 1 knee-high graduated compression stockings (13-20 hPa). Given for 14 days, and worn for a minimum of 6 hours per day. Cross over study, so half the participants were randomised to receive this treatment first, prior to the 7 day washout period.	Placebo: regular knee-high stocking used as a “reference” stocking, providing <10hPa. Very similar in appearance. Given for 14 days, and worn for a minimum of 6 hours per day. Cross over study, so half the participants were randomised to receive this	At end of double cross-over treatment period (35 days)	Patient assessed symptoms: global discomfort in legs, pain, heavy legs, cramps, swelling in ankles, mood, daily work activity. Adverse events.	not stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	are given for the lack of full cross-over results for the other variables. This opens up the risk of publication bias and reduced confidence in the validity of the presented findings. All that is stated is that the global discomfort, pain, heavy legs, cramps and swelling measured at the end of the cross-over stage were "similar".		popliteal junctions, obstacles or reflux in the deep venous network. Use of Calcium channel blockers, anti-coagulants, diuretics, anti-inflammatory drugs, Vitamin C, recent hormonal treatment, recent phlebotonic or pain medications, recent elastic compression and indications for sclerotherapy or surgery. **Baseline characteristics:** No significant differences between the two randomised groups (control first versus intervention first) for age, weight, height, professional status, risk factors or past medical history. No baseline differences in outcome variables.		treatment first, prior to the 7 day washout period.			

Results: NOTE: Full cross-over results are given for mood and daily work activity only. For all others, results pertain to those recorded at the end of the first phase (before cross-over). All that is stated is that the group differences in global discomfort, pain, heavy legs, cramps and swelling measured at the end of the cross-over stage between the two treatment groups were "similar" to those at day 14.

	Compression [mean VAS (sd)]	**Placebo** [mean VAS (sd)]	**p value**
Global painful discomfort in the legs during days 7-14	1.8 (1.7)	3.1 (2.1)	<0.05
Global painful discomfort in the legs at day14	1.4 (1.8)	2.9 (2.1)	<0.01
Mood (unclear if a high score represents good or bad mood)	1.1 (1.7)	1.5 (1.9)	
Daily work activity (unclear if a high score represents high or low activity)	1.1 (1.6)	1.6 (1.8)	
	Compression [count with no change or a deterioration]	**Placebo [count with no change or a deterioration]**	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Pain at day 14	27/61	37/53	0.0215
Heavy legs at day 14	20/59	35/54	0.0025
Cramps at day 14	37/61	44/55	0.0379
Ankle swelling day 14	35/61	43/53	0.0240

No outcome reporting for paresthesia, leg volume, changes in venous refilling time or venous pump power, except that no difference between compression and placebo.

Adverse events were reported as being significantly worse for those using the placebo stockings – slipping sensation on the leg, warming sensation, a feeling of pressure on the legs.

Author's conclusions: The wearing of class 1 graduated compression knee-high stockings (10-15 mmHg at the ankle) for a 15 day treatment period results in a significant improvement in the symptomatology and in the quality of life criteria in patients presenting with early-stage CVD of the lower extremities.

Table 51: Junger 1996[126]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Junger M, Galler S, Klscz T, Steins A, Hahn M. Improvement of cutaneous microangiopathy by compression therapy in chronic venous insufficiency. Phlebology Suppl. 1996; 1: S10-S13.	Cohort study.	20	**Inclusion:** Chronic Venous Insufficiency (CVI) class I (n=7) and II (n=13), according to Widmer's classification; **Baseline characteristics:** Gender: 10 men; 10 women; mean age 54.9 years(9.5); 3 with previous DVT; all with ankle brachial index>1.0; all had reduced venous refill time (20(12) seconds); Doppler showed incompetence of: • deep veins in 7 patients • superficial veins in 12 patients • perforating veins in 6 patients.	2 weeks of short-stretch bandaging, followed by 2 more weeks with class II compression stockings (the 3 with previous DVT used class III).	Before and after design.	2 weeks and 4 weeks.	Patient assessed symptoms: pain, tautness, swelling, itching, and feelings of cold, heat and restriction (on a scale of 0-3 (max complains)	None stated
Results: Reported that subjective treatments in all patients decreased during treatment, except for the feeling of coldness, which increased again during the second part of the study using compression stockings. There were no complaints by patients about feelings of constriction during the second part of therapy. No numerical data presented.								
Author's conclusions: No relevant conclusion with reference to patient symptoms.								

1

Table 52: Krijnen 1997[139]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Krijnen RMA, de Boer EM, Ader HJ, Osinga DSC, Bruynzeel DP. Compression stockings and rubber floor mats: do they benefit workers with chronic venous insufficiency and a standing profession? JOEM 1997; 9: 889-894.	Quasi-randomised controlled trial. The truly random part was the allocation to treatment and control groups. No details of randomisation method used. No evidence given of allocation concealment. There was a further, non-random splitting of the treatment patients to the two treatments – compression stockings or the use of rubber mats to stand on. This was decided by the safety and hygiene conditions of the factory concerned. In 10 factories compression stockings were used, and in 4 rubber mats were used. It is conceivable that this could cause bias by the compression group being from a certain type of factory (specific hygiene and safety conditions) and the placebo group being from any type of factory (perhaps those working in a certain type of factory – i.e. heavy industry - would have different risk	114 in total. 101 in the control (n=50) and compression (n=51) groups. In the compression group one refused to wear hosiery and a further 5 were lost to follow-up, for “unrelated reasons”. A further 15 stopped wearing the stockings every day during the study, for reasons including poor fit or skin problems. 16 were lost to follow-up from the control group.	All male factory workers with a predominantly standing job from 14 factories. All with evidence of chronic venous insufficiency (CVI). 40 had complications including trunk varicosis, lipodermatosclerosis, hyperpigmentation, atrophy blanche or dermatitis. None had leg ulcers. **Inclusion:** Evidence of CVI by physical examination, Doppler ultrasound investigation and light reflective rheography. Standing factory job. **Exclusion:** Individuals with only intracutaneous or only a few small varicose veins. **Baseline characteristics:** No comparison of anthropometric baseline characteristics. At baseline, the compression and control groups were similar for proportion having pain, with 10/30 in pain in the intervention group and 13/34 in the control group [estimated from graph] (no statistical analysis done), and the	Below knee class II (30-32 mmHg) seamless compression stockings. Used during working hours only.	Not described, but appears to be no treatment.	3 months	Patient assessed symptoms Adverse events	not stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	factors). However this would probably be a small effect as only 13 subjects out of 64 in the treatment group were put in the mat group. Only results for compression versus control are included in this evidence table.	**No ITT performed so analysis restricted to the 30 who wore the stockings almost every day, and the 34 in the control group who attended follow-up.**	control group [19/34, estimated from the graph] had a slightly lower proportion of people than the compression group [21/30] with a tired feeling at baseline. This slight difference will have favoured the control group, and thus does not invalidate the post-intervention finding that the compression group had a lower proportion of people with tired legs than the control group.					

Results: Post-test results given. Despite the lack of confirmation that the groups were similar at baseline for the variables below, the differences seen are unlikely to have led to a bias favouring compression. In particular, for the tired feeling, less control were in pain at baseline which would favour the control group.

	Compression	Control	p value
Patients with complaints of tired legs (proportion of subjects) at 3 months	8/30	18/34 (estimated from graph)	<0.005
Patients with complaints of pain (proportion of subjects) at 3 months	2/30	12/34 (estimated from graph)	<0.05
Patients with overall decrease in complaints at 3 months	17/30 For the 15 not wearing stockings every day: 4/15	4/50 (16 were reported lost to follow-up, and no ITT was done, so this may be a typographical error, and the correct result may be 4/34).	
Patients in favour of continuing stockings beyond study duration.	26/45		

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse events Reasons for non-compliance (only the 15 who did not wear the stockings everyday were asked. Each person could give only one reason each) itch red and swollen skin too tight	2/15 2/15 5/15							
Author's conclusions: Compression stockings appeared to be superior [....] with regard to applicability, [and] diminishing subjective complaints....								

Table 53: Lurie 2011[154]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lurie F, Kistner RL. Trends in patient reported outcomes of conservative and surgical treatment of primary chronic venous disease contradict current practices. Annals of Surgery 2011; 254: 363-367.	Observational single group before-after study.	150 were originally selected. These were divided into two groups who both initially had compression therapy (one group later had endovenous radiofrequency ablation whilst the other continued with conservative treatment, and the results of these later treatments will not be included here). However, since the data were continuous it is not possible to combine the results for the initial compression phase, so data from the larger group of 121 patients is given.	Consecutive patients with primary CVD were selected according to the criteria below. **Inclusion:** confirmed primary aetiology; unilateral involvement; great saphenous vein reflux; C2-C4; no use of compression for at least one year. **Exclusion:** CEAP stages C5-6; small saphenous vein involvement; current or recent use of compression; non-compliance with compression therapy; difficulty completing quality of life form; problems with English language comprehension. **Baseline characteristics:** Gender: 38% male; Age: mean age 54.4(11.7); CEAP stage: C2: 32.2%; C3: 24%; C4: 43.8%;	Compression therapy by 20-30mmHg knee-high graduated compression stockings given for 2 to 6 weeks. Lifestyle advice (weight loss, exercise and frequent leg elevation) ALSO given.	Pre versus post (2-6 weeks of treatment).	2-6 weeks.	Patient reported quality of life: Disease specific SQOR-V form Patient assessed symptoms: Symptom score	None stated

Results: mean (sd) given. N=121

	pre-compression	post-compression	p value
Symptom score (this is made up of part of the SQOR-V form, comprising severity of pain, heaviness, itching, night cramps, heat or burning, tingling,	16.9(9.8)	6.3(5.8)	not given

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
throbbing, restless legs, swelling. The symptom score is the sum of the scores of these 9 symptoms, each on a 6 point scale; a higher score indicates worse symptoms, with 54 the worst score)								
SQOR-V form (this is made up of several domains, with higher scores indicating worse disease specific QoL; 190 is the maximum score)			62.5(20.6)		48.9(17.9)		not given	
Author's conclusions: compression therapy selectively improves some symptoms....the QOL outcomes of compression therapy were better than the symptom response.								

1

Table 54: Motykie 1999[176]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Motykie GD, Caprini JA, Arcelus JI, Reyna JJ, Overom E, Mokhtee D. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. Dermatol Surg 1999; 25: 116-120	Before-after design observational trial, without control group. Therefore subject to uncontrolled threats to internal validity, such as time effects, placebo effects etc.	112. Those with bilateral symptoms included, but unclear how many.	**Inclusion:** Patients with chronic venous insufficiency (CVI). **Exclusion:** patients currently wearing compression stockings. **Baseline characteristics** Gender: 95 females, 17 males; Age: range 27-85 years (mean 46.8); No prior CVI or varicose veins treatment: 95/112. Prior treatment 17/112 • 11/17 sclerotherapy • 6/17 stripping surgery. Flawed statistics provided for CEAP class. Authors gave percentages of participants with the main symptom characteristic of each CEAP class which is not helpful as some symptoms will span multiple CEAP grades (i.e. instead of “swelling” indicating those with swelling but NOT pigmentation or ulceration, which would be equivalent to CEAP3, the swelling statistic included any of those also with pigmentation and ulceration, which was therefore no longer equivalent to CEAP3).	30-40 mmHg compression stockings for 16 months. Hours per day and night-use unclear. The stockings varied • 36% thigh lengt, • 17% mid-thigh length • 47% knee or calf length	Post treatment compared to pre-treatment.	1 month and 16 months (treatment continued to end of follow-up).	Patient assessed symptoms Adverse events	None stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results: mean (sd) given. Patients with bilateral symptoms given were given bilateral stockings, but number with bilateral symptoms unknown. Hence unclear how many data points there were.

Patient assessed symptoms (1-5 scale, with 1=minimal problem and 5=maximal problem)	**pre-compression**	**1 month post-compression**	**16 months post-compression**	**p value (Wilcoxon signed ranks test used, despite the presentation of sds)**
swelling	2.45(1.25)	1.47(0.83)	1.13(0.51)	P<0.001 for comparison between baseline and 1 month for all variables. P<0.0001 for comparison between baseline and 16 months for all variables.
pain	2.94(1.29)	1.77(1.09)	1.38(0.69)	
discolouration	2.76(1.29)	2.23(1.22)	1.81(0.99)	
cosmetic problems	3.03(1.41)	2.50(1.41)	1.98(0.99)	
activity tolerance	2.33(1.35)	1.71(1.19)	1.38(0.73)	
depression	1.72(1.12)	1.42(0.87)	1.29(0.81)	
sleep problems	2.00(1.25)	1.46(0.99)	1.24(0.63)	
Adverse events (scale the same as for patient assessed symptoms)				
numbness	NA	1.41(1.20)	1.20(0.92)	NA
Sweating		1.45(1.00)	1.23(0.83)	
Itchiness		1.40(0.97)	1.14(0.78)	
new pain		1.44(1.20)	1.12(0.80)	
Compliance (still wearing stockings)		92/112	78/112	

Author's conclusions: Therapeutic graduated compression stockings are an effective treatment for CVI of the lower extremities

1 **Table 55: Pannier 2007**[201]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pannier F, Hofffmann B, Stang A, Jockel KH, Rabe E. Prevalence and acceptance of therapy with medical compression stockings. Phlebologie 2007; 36: 245-249.	Cross-sectional questionnaire/ interview study.	3072	**Inclusion:** Randomly recruited from a German city and environs; included ALL residents, regardless of health status; urban to city ratio of 2:1; 59% response rate; demographics representative of the general German population; **Baseline characteristics:** mean BMI: 25.6(4.8); 890 described as having varicose veins. 961 had history of chronic venous sufficiency (CVI) at CEAP stages C2-6: • C2: 439/961 • C3: 412/961 • C4: 88/961 • C5: 19/961 • C6: 3/961.	Patients with a history of varicose veins were asked about their use of medical compression stockings (MCS).	NA		Patient assessed symptoms Adverse events	None stated

Results: 10.3%% (n=316) of all sample with CEAP stages C2-6 had used MCS (32.9% of those with C2-C6). At the time of interview, 210/316 (66.5%) who had ever received MCS were not wearing them at the time of interview, and had not worn them in the last 4 weeks, indicating a compliance figure of 33.5%.

The groups who had used them in the last 4 weeks and not used them in the last 4 weeks differed in terms of the proportions from each CEAP class, with the most severely affected tending to be more compliant:

CEAP	**Medical compression stockings used, but not in last 4 weeks**	**Medical compression stockings used in last 4 weeks**
C2	96/210 (21.9%)	26/106 (5.9%)
C3	78/210 (18.9%)	50/106 (12.1%)

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C4		28/210 (31.8%)			20/106 (22.7%)			
C5-C6		8/210 (36.4%)			10/106 (45.5%)			
For those who used MCS currently, patients usually wore their MCS 5 or more days per week (73%) and for 8 or more hours per day (89.4%). 71.3% of the interviewed participants using MCS said their medical condition had improved with MCS therapy. This included: • reduction in swelling (84.2%) • reduction in heaviness (89.4%) • reduction in leg pain after prolonged standing (60.9%) • reduction in tension in the legs (78.9%) Most patients could not remember the compression class, but available evidence suggested: • class 1: 13 • class II: 149 • class III: 26 The types were: • compression tights: 34% • thigh compression stockings: 23% • lower leg compression stockings: 41.1% Adverse events were reported as: • pruritis (8.4%) • eczemas (1.6%) • constrictions under the MCS (8.4%) • slipping of stockings (3.6%)								
Author's conclusions: An improvement of their condition was attributed to [MCS] by 80% of patients.								

Table 56: Raju 2007[217]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Raju S, Hollis K, Neglen P, Mississippi F. Use of compression stockings in chronic venous disease: patient compliance and efficacy. Ann Vasc Surg 2007; 21: 790-795	Case series. Extremely limited methodology in terms of being open to multiple risks of bias.	3144	**Inclusion:** Stated that "new" chronic venous disease (CVD) cases, but then also stated that they had been under care with GP or other specialists for variable periods of time; **Baseline Characteristics:** • Age: median 58 (range 17-92); • Gender: Male: Female =1:2 • CEAP stages ○ CEAP 0-2: 67% ○ CEAP 3: 22% ○ CEAP 4: 4% ○ CEAP 5: 4% ○ CEAP 6: 3% • Aetiology was primary in 58% and post-thrombotic in 42%.	None. This was an observational study of CVD patients, and only 37% were using stockings.	NA		Compliance	None stated

Results:

21% of patients reported full "compliance". 12% used them most days and 4% some days. The other 63% did not use the stockings at all or had abandoned them after a trial period in the past. Compliance did not differ according to CEAP class, gender or previous DVT. Compliance did improve with longer duration of treatment

Reviewer's comment: As not all the patients in the study had been prescribed stockings, these daily use figures of 21%, most days use figures of 12% and occasional use values of 4% do not really equal compliance, as compliance must make use of the number prescribed them as the denominator. Clearly a patient never prescribed a treatment cannot be described as non-compliant. As only 75% of the patients had been recommended stockings by a doctor, the true full compliance figure would be 21/0.75= 28%; full and partial compliance would be (21+12)/0.75=44% and full, partial and minimal compliance would be 21+12+4)/0.75=49.33%.

	Primary reasons for non-use of stocking, of those that were recommended stockings by their doctor
unable to state a reason	40%

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
lack of efficacy	20%							
poor fit/cut off circulation	17.3%							
too hot	9.3%							
soreness	2.67%							
needs application assistance	2.67%							
cosmetic reasons	2.67%							
itching/dermatitis	2.67%							
worsening of symptoms	1.33%							
lack of self-discipline	0.67%							
Cost	0.53%							
Work-related	0.27%							
Author's conclusions: Non-compliance is very high in patients with CVD regardless of age, sex, aetiology of CVD, duration of symptoms or disease severity.								

G.4.2 Compression vs. interventional treatment

Table 57: Michaels 2006[170]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Michaels JA, Brazier JE, Campbell WB, MacIntyre JB, Palfreyman SJ, Ratcliffe J. Randomised clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. British Journal of Surgery 2006; 93: 175-181
AND
Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, Rigby K.</td>
<td>RCT. Computer randomisation and group allocation by telephone. Thus allocation concealment very likely.
No blinding reported for patient or researchers, or assessment of the outcomes relevant to the review question.
Intention to treat carried out in terms of</td>
<td>246 randomised. Although there were a number of bilateral cases, the total number of legs is not reported. In the surgery group there were 18.1% with bilateral surgery. However it appears that randomisation was only by the worst leg, and so results relating to the better leg are not included here.
Of the 122 randomised to conservative treatment, all received treatment. 21 lost to follow-up at 1 year, leaving 101 for analysis. A</td>
<td>Taken from consecutive referrals to vascular units at two large hospitals in the UK.
Inclusion: primary varicose veins with sapheno-femoral or sapheno-popliteal reflux.
Exclusion: co-existing disease or disability precluding surgery; complications of varicose veins; veins < 5mm in diameter in lower thigh.
Baseline comparison. Reported no group differences.
<table>
<tr><th></th><th>conservative</th><th>surgery</th></tr>
<tr><td>F:M</td><td>87:35</td><td>83:41</td></tr>
<tr><td>Age</td><td>49.5</td><td>49</td></tr>
<tr><td>height</td><td>168</td><td>167.8</td></tr>
<tr><td>BMI</td><td>26.9</td><td>26.4</td></tr>
<tr><td>smokers</td><td>21.3%</td><td>26.6%</td></tr>
<tr><td>Family history of VV.</td><td>70.5%</td><td>73.4%</td></tr>
<tr><td>Family history of leg</td><td>7.4%</td><td>16.1%</td></tr>
</table>
</td>
<td>Use of compression hosiery, alongside lifestyle advice relating to exercise, leg elevation, and weight / diet management.
Duration of treatment unclear.</td>
<td>Stripping surgery, done under general anaesthetic and usually as a day case.
For patients with affected great saphenous veins(GSV): flush ligation at the saphenofemoral junction, with stripping of the GSV to knee level, with multiple phlebectomies.
For patients with affected short saphenous veins(SSV): sapheno-popliteal</td>
<td>1 and 2 years.</td>
<td>Quality of life
Patient assessed symptoms
Patient satisfaction
Adverse events</td>
<td>NHS HTA programme.</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). Health technology assessment 2006; vol 10: number 13. This second article covers the same trial with the same patients, and contains the same information as the first study, with some small additions (in red).	those refusing the randomised treatment being kept in that group and analysed. However no imputation carried out for those failing to attend follow-ups.	further 63 also discontinued compression over the following 3 years, opting for surgery. However these were kept in the analysis in the conservative treatment group, as per ITT. Of the 124 allocated to surgery, 109 received surgery. 9 refused surgery and had conservative treatment instead, and 6 deferred. These 15 were kept in the group, and analysed, with ITT. 43 lost to follow-up at 1 year, and so there were 81 available for analysis at 1 year. Some of the 43 lost to follow-up were contacted and reported that their	ulcers				ligation at the sapheno-femoral junction, with stripping of the SSV in some patients, with multiple phlebectomies.			
			Previous pregnancies (mean)	2.1	2.1					
			SF-6D	0.74(0.11)	0.73(0.1)					
			EQ-5D	0.77(0.18)	0.76(0.19)					

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		withdrawal was not due to lack of efficacy or adverse events, but mostly because they were well.						

Results:

Outcome	**Conservative**	**Surgery**
SF-6D 1 yr mean(sd)	0.73(0.11) n=98	0.77(0.10) n=75
SF-6D 2 years mean(sd)	0.72(0.13) n=47	0.78(0.10) n=44
EQ-5D 1 yr mean(sd)	0.78(0.18) n=101	0.87(0.14) n=78
EQ-5D 2 years mean(sd)	0.85 (0.17) n=44	0.84 (0.21) n=34
SF-36	no overall scores given – only sub-scales given	
Aching (proportion same or worse) at 1 yr	72/97	15/75
heaviness (proportion same or worse) at 1 yr	52/97	9/75
itching (proportion same or worse) at 1 yr	42/97	10/75
swelling (proportion same or worse) at 1 yr	31/97	8/75
cosmetic concerns (proportion same or worse) at 1 yr	75/97	13/75
Patient dissatisfaction at ?1 year (follow-up point unclear)	53/107	3/65
Adverse events		
neural damage (footdrop resolving in 8/52)	0/122	1/124
post-op pain	0/122	3/124
phlebitis	3/122	0/124

G.5 Chapter 9 – interventional treatment

G.5.1 Stripping surgery vs. foam sclerotherapy

Table 58: Abela 2008[2]

<table>
<tr><th>Reference</th><th>Study type</th><th>No of patients</th><th colspan="4">Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="3">Abela R et al. Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard and invagination stripping: a prospective clinical series. EUROPEAN JOURNAL OF VASCULAR & ENDOVASCULAR</td><td rowspan="3">RCT, UK.
Allocation concealment via sealed envelopes. Randomisation method unclear.
[Technical failures occurred in 2 patients in the standard stripping group, 4 patients in the invagination group, and 3 patients in the foam sclerotherapy group. [BUT no. of people who withdrew from study was not described]</td><td rowspan="3">90 consecutive limbs of 82 patients with incompetence of the GSV resulting from varicose veins.
(74 of the 82 patients had unilateral saphenous incompetence and 8 had bilateral incompetence)</td><td colspan="4">Inclusion: Patients >18 years old with CEAP 2 and 3 symptomatic primary varicose veins (i.e. with SFJ and GSV reflux, confirmed by diagnostic duplex ultrasound assessment.
Exclusion: Not disclosed
Baseline characteristics:</td><td rowspan="3">Stripping surgery via 1) Standard stripping (using a Babcock-type flexible stripper) or 2) Invagination technique.
Tumescent anaesthesia applied along the length of the GSV prior to stripping. All legs dressed post-operatively with foam strip padding applied externally over the length of the GSV track, which was secured using an elastic adhesive bandage. 1 day post op, drains removed, legs dressings taken down and replaced</td><td rowspan="3">Reverse foam sclerotherapy: 3ml of 1% sodium tetradecyl sulphate (Fibrovein®) mixed with 3ml air resulting in 6ml foam; injected into collapsed vien via the angiography catheter as this was withdrawn along the length of the vein (hence ’reverse foam’). Proximal GSV tied 5cm distal to its cut end and redundant few cm of vein excised. Complete filling of vein</td><td rowspan="3">2 weeks post treatment.</td><td rowspan="3">Post-op thigh bruising (reported by patients and observers).
Adverse events, including post-procedure pain (as indicated by no. of patients using analgesia).</td><td rowspan="3">Not stated</td></tr>
<tr><td></td><td>Standard stripping</td><td>Invagination stripping</td><td>Reverse foam sclerotherapy</td></tr>
<tr><td>Mean age (range)</td><td>46 (18-66)</td><td>47 (25-67)</td><td>45 (22-66)</td></tr>
</table>

Reference	Study type	No of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SURGERY. 2008;36(4):485-490.			F:M ratio	17:13	15: 15	22: 8	by Class II graduated compression stockings worn continuously until follow-up at Day 15.	checked by ultrasonography. [NOTE: to ensure uniformity between the procedures, tumescent anaesthesia applied along the length of the GSV prior to stripping.] All legs dressed post-operatively with foam strip padding applied externally over the length of the GSV track, which was secured using an elastic adhesive bandage. 1 day post op, drains removed, legs dressings taken down and replaced by Class II graduated compression stockings worn continuously until			

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					follow-up at day 15.			

Results

Outcome	**Standard stripping (n= 30 legs)**		**Invagination stripping (n= 30 legs)**		**Reverse foam sclerotherapy (n= 30 legs)**	
Post-op bruising	**Patient (%)**	**Observer (%)**	**Patient (%)**	**Observer (%)**	**Patient (%)**	**Observer (%)**
None	13	20	13	13	67	77
Moderate	50	73	70	80	30	23
Significant	37	7	17	7	3	0
Post-procedure pain	Use of analgesic post-op (% patients)					
No	5/30 (17%)		7/30 (23%)		23/30 (77%)	
Occasional	25/30 (83%)		19/30 (63%)		7/30 (23%)	
Regular	0		4/30 (13%)		0	
Adverse events	No clinically detectable adverse events attributable to the use of foam sclerotherapy were reported post-operatively or during the follow-up period.					

Author's conclusions: Standard stripping of the GSV and invagination stripping are not associated with **major discomfort and problems in the early post-op period.** SFJ ligation and GSV reverse foam sclerotherapy yielded **greater patient satisfaction** with less post-op bruising and **discomfort** and reduced analgesic requirements. (NOTE: data not reported in paper for the outcomes in bold)

Table 59: Bountouroglou 2006[30]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Bountouroglou DG, Azzam M, Kakkos SK, Pathmarajah M, Young P, Geroulakos. Eur J Vasc Surg 2006; 31: 93-100.</td>
<td>RCT.
Allocation decided by random drawing of sealed envelopes. With this form of randomisation, allocation concealment likely initially, but less likely as study goes on (see notes for Liu et al. 2011). No mention of blinding.</td>
<td>60 patients</td>
<td>Inclusion: Symptomatic primary varicose veins due to GDV incompetence; no previous treatment for varicose veins; suitability for day case surgery.
Exclusion: primary varicosities involving both the GSV and SSV; prev. var. Veins surgery or sclerotherapy; history of DVT or risk factors for DVT; Coagulopathy; PVD; relevant allergies; malignancy; pregnancy.
Baseline characteristics:
<table>
<tr><th></th><th>Stripping</th><th>Sclero</th></tr>
<tr><td>Age</td><td>20-76</td><td>21-72</td></tr>
<tr><td>Female</td><td>60%</td><td>47%</td></tr>
<tr><td>C2</td><td>8/28</td><td>11/30</td></tr>
<tr><td>C3</td><td>14/28</td><td>8/30</td></tr>
<tr><td>C4</td><td>6/28</td><td>7/30</td></tr>
<tr><td>C5</td><td>1/28</td><td>3/30</td></tr>
<tr><td>C6</td><td>1/28</td><td>1/30</td></tr>
<tr><td>VCSS</td><td>2-16</td><td>2-13</td></tr>
</table>
</td>
<td>Ligation performed at SFJ. GSV stripped from SFJ to a level just below the knee. General anaesthetic used.
Multiple phlebectomies also performed.
Compression bandages applied post op and then</td>
<td>Ligation performed as for stripping under LA. Varicosities injected with 6mL of a 3% STD sclerosant (foam), then compression applied using foam pads and a class II compression stocking for 2 weeks.</td>
<td>3 weeks and 3 months</td>
<td>AVVQ
VCSS
Adverse events
Treatment failure</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				replaced by a class 1 elastic stocking for 3 weeks. Randomised n=30; 2 did not receive treatment at all (1 moved, 1 moved out of area). 28 attended 3 week assessment. 5 lost to 3 month assessment (no reasons given).	Randomised n=30; All received treatment. 30 attended 3 week follow-up. 1 lost to 3 month follow-up			

Results:

	Stripping surgery (n=28)	Foam sclerotherapy (n=30)

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

HRQoL – AVVS [median	pre:26.1 post:14.1	pre:15.4 post:9.3
VCSS [median (range)] CEAP [median (range)]	3(0-4) 1(0-5)	1(0-5) 1(0-5)
Adverse events (time not stated)		
DVT	0/28	0/30
PE	0/28	0/30
phlebitis	0/28	3/30
skin pigmentation	1/28	2/30
neural injury	2/28	0/30

Author's conclusions: US guided sclerotherapy combined with sapheno-femoral ligation was less expensive, involved a shorter treatment time and resulted in more rapid recovery. .

1

Table 60: Figueiredo 2009[97]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Figuerido M, Araujo S, Barros N, Miranda F. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. Eur J Vasc Surg 2009;	RCT. Allocation decided by random drawing of papers from a box. With this form of randomisation, allocation concealment likely initially, but less likely as study went on (see notes for Liu et al. 2011). No mention of blinding.	60 patients	Patients attending an angiology and vascular surgery outpatient clinic. **Inclusion:** No previous treatment of varicose veins; age 18-70; C5; **Exclusion:** History of DVT, thrombophilia, allergy to polidocanol, bronchial asthma, post-thrombotic syndrome; severe systemic disease; immobility; pregnancy; peripheral arterial insufficiency; ABI<0.8); LL oedema; diabetic foot; patent foramen ovale on echocardiography. **Baseline characteristics:**	Saphenofemoral or saphenopopliteal ligation combined with saphenous stripping and phlebectomy for varicose saphenous tributaries and ligation of incompetent perforating veins. All surgery done in one session. Regional anaesthesia used. Inelastic	Injections in standing. Injections of foam made into the saphenous trunk. Accessory veins cannulated using 25 gauge butterfly needles. Foam was polidocanol and air in a ratio of 1:4. The GSV received 8-10 ml with a polidocanol concentration of 3%, the small	1,2 and 6 months post intervention.	VCCS Adverse events treatment failure	None

	Stripping	Sclerotherapy
Age	49(29-72)	53(25-76)
M:F	21:79	15:85
pre pain score	1.97(0.19)	1.81(0.4)
pre oedema score	1.66(0.48)	1.70(0.47)
pre inflammation score	1.55(0.63)	1.67(0.68)

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				bandages 2 days post op and then 30-40 mmHg below knee compression for 2 months. 30 randomised. Unclear how many received surgery, but 1 lost to follow-up (reasons not given)	saphenous vein 5ml at a concentration of 1 or 3%, the accessory veins 5ml at a concentration of 1% and perforating veins 1-2 ml at a concentration of 1%. Foam progress along veins imaged with US. Maximum bolus of 10ml in one session. Sessions repeated as needed every 30 days up to			

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					a maximum of 3 (average sessions per patient were 2.1). After 15 mins of compression of the SFJ or SSV, the limb bandaged using an inelastic bandage for 3-5 days. Then 30-40 mmHg below knee compression for 3 months. 30 randomised. Unclear			

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					how many received surgery, but 3 lost to follow-up (reasons not given)			

Results: mean (sd)

	Stripping surgery (n=29)	Foam sclerotherapy (n=27)	
VCSS pain 30 days	0.93(0.53)	0.89(0.51)	
VCSSpain 60 days	0.79(0.49)	0.59(0.50)	
VCSS pain 180 days	0.72(0.53)	0.56(0.51)	
VCSS oedema 30 days	0.69(0.60)	0.70(0.54)	
VCSS oedema 60 days	0.59(0.63)	0.56(0.64)	
VCSS oedema180 days	0.55(0.63)	0.48(0.64)	
VCSS inflammation 30 days	0.76(0.44)	0.89(0.32)	
VCSS inflammation 60 days	0.72(0.45)	0.89(0.32)	
VCSS inflammation180 days	0.72(0.45)	0.89(0.32)	
Adverse events neurological (subjective)	6/29	0/27	
Reflux/recanalisation	3/29	6/27	

Author conclusions: US guided foam sclerotherapy is a safe and effective option for patients with chronic venous disorders.

Table 61: Kalodiki 2011[129]21

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Kalodiki E, Lattimer C, Azzam M, Shawish E, Bountouroglou D, Geroulakos G. Long term results of a randomised controlled trial on ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation vs. standard surgery for varicose veins. Journal of vascular surgery; 2011 (in press).
NB This article in press has many typos and errors.</td>
<td>RCT.
Patients selected by drawing sealed envelopes. For impact of this on likelihood of adequate allocation concealment please see notes on Liu et al. 2011. Initially only the most symptomatic leg was randomised in bilateral patients. However if varicose veins developed in the contralateral limb this was included and given the same randomisation.</td>
<td>73 patients (82 legs).</td>
<td>Inclusion: Patients with primary symptomatic varicosities involving the GSV, without previous treatment and suitable for day case surgery.
Exclusion: Primary varicosities involving the GSV and saphenous vein (???), previous surgery or sclerotherapy for varicosities, past DVT, Coagulopathy, PVD, relevant allergies, malignancy or pregnancy.
Baseline characteristics: Median (IQR)
<table>
<tr><th></th><th>Stripping</th><th>Sclerotherapy</th></tr>
<tr><td>Age</td><td>49(29-72)</td><td>53(25-76)</td></tr>
<tr><td>M:F</td><td>21:79</td><td>15:85</td></tr>
<tr><td>C2</td><td>19/43</td><td>18/39</td></tr>
<tr><td>C3</td><td>11/43</td><td>10/39</td></tr>
<tr><td>C4</td><td>11/43</td><td>7/39</td></tr>
<tr><td>C5</td><td>1/43</td><td>3/39</td></tr>
<tr><td>C6</td><td>1/43</td><td>1/39</td></tr>
<tr><td>VCSS</td><td>5(3-12)</td><td>4.5(2-15)</td></tr>
<tr><td>VSDS</td><td>1 (IQR unclear)</td><td>1 (IQR unclear)</td></tr>
<tr><td>AVVQ</td><td>16.32 (IQR</td><td>12.28 (IQR unclear)</td></tr>
</table>
</td>
<td>Conventional high DFL stripping surgery combined with multiple phlebectomies using Muller hooks. General anaesthesia used. Immediately post-op compressive bandages applied, which were changed for a compressive stocking before</td>
<td>Foam sclerotherapy with 6mL of 3% Sodium tetra decyl sulphate (STS) (1.2 mL of STS mixed with 4.8 mL of air) injected directly into the vein under US guidance. Post procedure a 18-24 mmHg thigh high graduated elastic compression stocking was</td>
<td>3 weeks, 3,6 and 12 months and yearly thereafter. Median follow-up was 5 years.</td>
<td>HRQoL – SF36 and AVVs.
Physician reported disease severity – CEAP, VCSS, VSDS.
Adverse events
Reflux</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			unclear) SF-36: No report on similarity. No data given but appear very similar on figure	discharge from the day ward. n=43 limbs (39 subjects)	applied. Patients worse this for 2 weeks continuously, and then 1 week in the day only for another week. Patients also told to walk for 2 miles / 2 hours daily n=39 limbs (34 subjects)			

Results: Median (IQR) given.

	Stripping surgery (n=43 legs)	**Foam sclerotherapy (n=39 legs)**	p
AVVQ at 3 years	8.94 (IQR unclear)	4.97(IQR unclear)	NS??
AVVQ at 5 years	5.45(IQR unclear)	7.345(IQR unclear)	0.015
SF-36	Data only given in figures, and p values only given in text. Reported that no		

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	difference between groups in changes on the physical(p=0.724) and mental scores(p=0.354)		
VCSS increase from baseline to 3 years VCSS increase from baseline to 5 years	1(0-9) very unclearly reported	1(0-9) very unclearly reported	**0.504**
VCSS absolute score at 3 years VCSS absolute score at 3 years	reported no diff between groups reported no diff between groups	**0.313** **0.104**	
VSDS at 3 years VSDS at 5 years	0.5(IQR unclear) 1.0(IQR unclear)	1.0(IQR unclear) 0.25(IQR unclear)	0.780 0.388
Adverse events			
thromoboembolism (DVT and PE)	0/43	0/39	
major neurologic event (i.e. stroke)	0/43	0/39	
skin pigmentation	2/43	1/39	
thrombophlebitis	0/43	3/39	
saphenous nerve injury	2/43	0/39	
hematoma	1/43	0/39	
skin ulcer	1/43	0/39	
Reflux at 3 years ABOVE KNEE* Reflux at 5 years ABOVE KNEE	7/26 9/26	11/33 13/33	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Reflux at 3 years BELOW KNEE Reflux at 5 years BELOW KNEE	14/26 9/26		19/33 14/33					
*cannot sum above and below knee data as some may be from the same subjects								
Author's conclusions: At 3 and 5 years of follow-up, the treatment was equally effective in the surgical and foam groups, as demonstrated with VCSS, VSDS and the SF-36...at 5 years the AVVQ was significantly better in the surgical group.								

Table 62: Liu2011[148]

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Liu X, Jia X, Guo W, Xiong H, Zhang M, Liu X, Du X, Zhang MH. Ultrasound-guided foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping: a prospective clinical study. International Angiology 2011; 30: 321-6.	RCT; China. Allocations placed in 60 sealed envelopes and then shuffled. Each recruited patient given one. Not stated if there was any patient blinding. Also no mention of assessor blinding. Although the method of allocation meant that group allocation was automatically concealed from the recruiter at first, it is possible that towards the end of recruitment it might become possible to predict the allocation of the next patient to be recruited (i.e. if after 50 patients it	60 patients randomised; 59 treated.	Patients undergoing treatment for varicose veins in a vascular surgery clinic; 26 men and 34 women; CEAP ranged from C2-C6 (no breakdown given). Median age 49 (range 37-66). **Inclusion:** symptomatic primary varicose veins with primary SFJ and GSV reflux, as shown by duplex (reflux duration >0.5 secs after calf compression-release manoeuvres). **Exclusion:** None given **Baseline characteristics:** Demographics not given. No breakdown of any characteristics done by group. However, groups matched for CEAP median (range): both 4(2-6). AVVQ median (range) was similar: Sclerotherapy: 15(11-26); surgery: 19(14-29).	N=30 Stripping surgery, using a flexible intraluminal stripper to strip from groin to knee. Preceded by flush ligation, division of tributaries. Varicosities also treated by phlebectomy. Done under GA. All patients with residual varicose veins in both groups received additional foam sclerotherapy as outpatients (not stated when). 30 randomised; 29 received treatment (patient changed mind); 1 loss to follow-up at 3 months (didn't	N=29 Ultrasound-guided foam obliteration of the GSV. After SFJ ligation, 6mL sclerosing foam (1 part of 1% Lauromacrogol [Polidocanol] and 4 parts of air) injected into GSV proximal cut end via 10mL syringe connected to a 21 gauge butterfly. Sclerosant foam flow monitored via US. Remnant trunks not filled with foam were punctured and filled with additional sclerosant. Done under GA . All patients with residual varicose veins in both groups received additional foam	3 months and 6 months post-op.	AVVQ Physician reported Adverse events treatment failure	None

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	was known that 28/30 stripping places had been already taken up, then it would be known that the probability of the next patient being a control patient would be 80%).			attend follow-up); No further loss to follow-up at 6 months.	sclerotherapy as outpatients (not stated when). 30 randomised; 29 received treatment; 2 loss to follow-up at 3 months (didn't attend follow-up); 2 further patients lost to follow-up at 6 months (didn't attend follow-up).			

Results:

	Stripping surgery (n=30)	**Foam sclerotherapy (n=29)**	p	
HRQL				
AVVQ median (range) 3 months	12(8-17)	9(5-16)	**no intergroup p value given**	
Physician reported outcomes				
CEAP median (range) 3 months	1(0-4)	1(0-3)	**no intergroup p value given**	
Adverse events				
groin hematoma	1/30	0/29		
neural injury	2/30	0/29		

Reference	Study type	No of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
thrombophlebitis			1/30	3/29				
skin pigmentation			1/30	2/29				
DVT			0/30	0/29				
PE			0/30	0/29				
Post op use of analgesia (any)			24/30	8/29				
No full obliteration 3 months (requiring second session of sclero)			3/28	3/28				
No full obliteration 6 months (requiring second session of sclero)			3/26	5/25				
Author conclusions: US guided sclerotherapy, combined with sapheno-femoral ligation involved a shorter treatment time, less post-operative discomfort and resulted in more rapid recovery compared to conventional GSV stripping.								

Table 63: Rasmussen 2011[221]

<table>
<tr><th>Reference</th><th>Study type</th><th>No of patients</th><th>Patient characteristics</th><th>Stripping surgery</th><th>Foam sclerotherapy</th><th>Endothermal ablation</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, and Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. British Journal of Surgery 2011;</td>
<td>RCT, Denmark.
2 private surgical centres.
Randomisation in blocks, but method not clearly described. Allocation concealment adequate via sealed envelopes.
No blinding reported.</td>
<td>500 patients were randomised
125 in each group. The results for endothermal laser ablation (n=125) and radio frequency ablation (n=125) have been combined in these results.
All received intervention except one patient (and 1 leg) in the</td>
<td>Inclusion: 18-75 years; symptomatic varicose veins; CEAP 2-4; Great Saphenous Vein(GSV) incompetence, defined by reflux >0.5secs on duplex; Bilateral treatment allowed so long as in same group. Patients with recurrent varicose veins also included if GSV preserved to the groin.
Exclusion: Duplication of the saphenous trunk or an incompetent anterior accessory saphenous vein; small saphenous vein reflux; previous DVT; history of arterial insufficiency: brachial pressure index <0.9, or both; axial deep vein insufficiency; tortuous GSV.
Baseline characteristics: mean (range). Authors report that groups well-matched.
<table>
<tr><th></th><th>Stripping surgery</th><th>UGFS</th><th>Endothermal (RF and EVLA)</th></tr>
<tr><td>N subjects</td><td>124</td><td>124</td><td>250</td></tr>
<tr><td>n legs</td><td>142</td><td>144</td><td>292</td></tr>
<tr><td>Age</td><td>50</td><td>51</td><td>51</td></tr>
</table>
</td>
<td>N=125 (143 legs).
Flush ligation of the GSV and division of all tributaries. Use of a PIN stripper to strip GSV to just below the knee.
Common procedures: Phlebectomies to remove varicosities in all groups. Compression applied post operativel</td>
<td>N=125 (145 legs)
Ultrasound-guided foam sclerotherapy [UGFS] (in the reversed Trendelenburg position); 3% polidocanol (Aethoxysclerol®); 2ml solution mixed with 8ml air. Retreatment allowed within 1 month.
Common procedures: Phlebectomies to remove varicosities in all groups. Compression applied via a 30 mmHg</td>
<td>N=250 (292 legs)
Endovenous Laser ablation (EVLA): Under duplex guidance with 980nm diode laser for 1^{st} 17 pts and then 1470 diode laser for the rest. Pulse mode was used in one centre but continuous used in the other. Cannulation just below the knee. The laser fibre was advanced</td>
<td>3 days, 1 month, 1 year.
It was intended to continue follow-up yearly for 5 years.</td>
<td>Quality of life: SF36 score and AVVQ.
Physician-reported outcomes: VCSS.
Treatment failure: defined as a patent GSV with reflux, or GSV not stripped successfully
Recurrence rates
Adverse events (including complications e.g. DVT and PE, post-intervention superficial</td>
<td>Public health Insurance Research Foundation of Denmark</td>
</tr>
</table>

Reference	Study type	No of patients	Patient characteristics				Stripping surgery	Foam sclerotherapy	Endothermal ablation	Length of follow-up	Outcome measures	Source of funding
98:1079–1087.		stripping and foam sclerotherapy groups, due to dizziness (stripping group) and patient's wishes (sclerotherapy group). At 1 year n=17 (21 legs) lost to follow-up or not seen in the sclerotherapy group, 37 (47 legs) in the endothermal group and n=27 (34 legs) in the stripping group.		(19-72)	(18-75)	(18-75)	y for all – at 20 mmHg for 2 weeks.	stocking for 2 weeks. Note that this group was given a different compression strength to the other two groups.	until 2cm below the sapheno-femoral junction, and then the GSV was ablated during withdrawal. **Endovenous radiofrequency ablation (EVRF):** catheter advanced under US guidance to 2cm below the sapheno-femoral junction. Then withdrawn, with temperatures maintained at 120		phlebitis, post-intervention pain during first 10 days) **Time to resume/return to normal activities and work**	
			%Female	77	76	77						
			CEAP2-3 (legs)	97	96	97						
			CEAP 4-6 (legs)	3	4	3						
			Previous surgery	8	4	8						
			GSV (diam) (mm)	7.8 (3-14)	8.7 (3-20)	7.8 (3-14)						
			Number of phlebectomies	15 (1-48)	15 (1-43)	15 (1-48)						
			surgeon's time (min)	32 (15-80)	19 (5-145)	32 (15-80)						

Reference	Study type	No of patients	Patient characteristics				Stripping surgery	Foam sclerotherapy	Endothermal ablation	Length of follow-up	Outcome measures	Source of funding
									degrees for 20 seconds per segment via a thermostat. **Common procedures:** Phlebectomies to remove varicosities in all groups. Compression applied post operatively for all – at 20 mmHg			

Results

	Stripping surgery (n=124 patients)	Foam Sclerotherapy (n=124 patients)	Endovenous Laser Ablation (n=125)	Radiofrequency ablation (n=125)
Treatment failure at 3 days[a]	4/141 legs	3/143 legs	0/143	0/146
Treatment failure at 1 month	3/135 legs	2/144 legs	1/144	0/141
Recurrent varicose veins at 1 year	16/108	17/123	7/121	6/124

Reference	Study type	No of patients	Patient characteristics	Stripping surgery	Foam sclerotherapy	Endothermal ablation	Length of follow-up	Outcome measures	Source of funding

Adverse events during 1st month

	Stripping surgery	Foam Sclerotherapy	Endovenous Laser Ablation	Radiofrequency ablation
Major:				
DVT (requiring treatment)	1/135	1/144	0/144	0/141
PE (requiring treatment)	0/135	1/144	0/144	0/141
Minor:				
Phlebitis	5/135	17/144	4/144	12/141
Infection	1/135	4/144	0/144	1/141
Paraesthesia	5/13	2/144	3/144	6/141
hyper pigmentation	6/135	8/144	3/144	8/141
Haemorrhage	1/135	1/144	1/144	0/141
Pain scores in first 10 days [mean(sd)] [VAS, 0-10, 10 worst]	2.25 (2.23)	1.60 (2.04)	1.21 (1.72)	2.25 (2.23)

SF-36 score (mean [SD]) at 1yr

	Stripping surgery	Foam Sclerotherapy	Endovenous Laser Ablation	Radiofrequency ablation
Physical functioning	92.82 (13.35)	91.33 (14.93)	92.02 (11.61)	92.22(12.62)
Role physical	93.41(16.32)	90.36 (20.56)	93.51(14.78)	94.65(10.64)
Bodily pain	88.77(17.11)	85.11(23.45)	88.43(19.55)	89.92(16.85)
General health	66.02 (14.00)	63.36 (18.31)	64.90(11.99)	67.08(11.82)
Vitality	76.99 (15.54)	73.20 (22.67)	77.74(14.03)	76(17.51)
Social functioning	95.19 (11.60)	93.10 (16.51)	96.51(11.22)	97.11(14.45)
Role – emotional	94.20 (14.02)	91.92 (17.11)	95.95(10.15)	94.5(11.02)
Mental health	85.92 (12.18)	84.58 (15.77)	87.70(10.51)	87.08(11.94)

<table>
<tr><th>Reference</th><th>Study type</th><th>No of patients</th><th>Patient characteristics</th><th>Stripping surgery</th><th>Foam sclerotherapy</th><th>Endothermal ablation</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="10">Summary Scores</td></tr>
<tr><td colspan="2">PHYSICAL 4 weeks</td><td colspan="2">48.14(7.21)</td><td colspan="2">49.2(7.56)</td><td colspan="2">47.68(6.95)</td><td colspan="2">49.88(7)</td></tr>
<tr><td colspan="2">PHYSICAL 1 year</td><td colspan="2">53.33(5.9)</td><td colspan="2">51.94(7.66)</td><td colspan="2">52.62(5.98)</td><td colspan="2">53.23(5.32)</td></tr>
<tr><td colspan="2">MENTAL 4 weeks</td><td colspan="2">55.15(7.81)</td><td colspan="2">56.1(7.51)</td><td colspan="2">55.55(8.21)</td><td colspan="2">55.57(7.38)</td></tr>
<tr><td colspan="2">MENTAL 1 year</td><td colspan="2">55.83(6.31)</td><td colspan="2">54.73(8.89)</td><td colspan="2">56.74(5.44)</td><td colspan="2">56.52(6.17)</td></tr>
<tr><td colspan="2">VCSS</td><td colspan="8">NOTE that only graphs were presented, and no actual data were provided.</td></tr>
<tr><td colspan="2">AVVSSS</td><td colspan="8">NOTE that only graphs were presented, and no actual data were provided.</td></tr>
<tr><td colspan="2">Time to return to normal activities (days) median(range)</td><td colspan="2">4 (0-30)</td><td colspan="2">1 (0-30)</td><td colspan="2">2(0-25)</td><td colspan="2">1(0-30)</td></tr>
<tr><td colspan="2">Time to return to work (days) median (range)</td><td colspan="2">4.3 (0-42)</td><td colspan="2">2.9 (0-33)</td><td colspan="2">3.6(0-46)</td><td colspan="2">2.9(0-14)</td></tr>
</table>

(a) Failure defined as patent GSV with reflux OR GSV not stripped successfully (unfair comparison as unstrapped GSV does not equal incompetent GSV, whereas unblocked GSV has to occur with reflux.

Table 64: Shadid2012[244]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shadid N, Ceulen R, Nelemans P. et al. Randomised clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein.	Multicentre randomised controlled trial. Computer generated randomisation with permuted blocks of eight.	460 randomised (233 to foam and 227 to surgery). 3 did not receive foam (2 declined and 1 not feasible) and 27 did not receive surgery (24 declined, 1 CVA, 1 surgeon not co-operating, 1 pregnancy). 17 lost to follow-up in Foam; 23 lost to follow-up in stripping. Resaons did not appear to be related to outcome.	Patients with primary GSV incompetence. All had C2-5EpAsPr **Inclusion:** presence of 1 or more symptoms in combination with incompetence of the SFJ and GSV, with reflux time of >0.5 sec; normal deep venous system **Exclusion:** active ulceration; contraindications to use of policodanol **Baseline characteristics:** Similar in both groups	Stripping surgery. Day case under GA or spinal. Ligation of SFJ and GSV divided and stripped to just below knee. Phlebectomies done as needed. Class II elastic stockings worn for 6 weeks.	Foam sclerotherapy. 3% policodanol in a foam (1:4 ratio of sclerosant to air). Class II elastic stockings worn for 6 weeks. NO CROSSECTOMY	2 years	Recurrence (clinical symptoms plus reflux) at 2 years Reflux (regardless of symptoms) at 2 years EQ-5D Symptoms Adverse events	None stated

	Foam	Surgery
Age	51.6(13.3)	50.7(13.4)
F:M	173:57	141:59
C2	86.5%	80%
C3	9.1%	11.5%
C4	9.1%	8%
C5	2.2%	3%

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results:

	Stripping surgery	Foam sclerotherapy	
Clinical recurrence (symptoms with accompanying reflux)at 2 years	16/177	24/213	
Clinical recurrence (symptoms with accompanying reflux)at 1year	13.8%	11.9%	
Clinical recurrence (symptoms with accompanying reflux)at 3 months	8.56%	10.8%	
Reflux at 2 years	18.2%	21.3%	
Reflux at 1year	23.1%	29.16%	
Reflux at 3 months	18.2%	21.3%	
Change in VCSS from baseline at 2 years	-1.75 (2.135)	-1.49 (2.135)	P=0.232 (no variances reported but common sd for each calculated as: 2.135)
Mean change in EQ-5D from baseline at 2 years	0.061 (0.211)	0.064 (0.211)	P=0.889 (no variances reported but common sd for each calculated as: 0.211)
More pain at 2 years	6/177	14/213	
More tired/heavy feeling at 2 years	5/177	6/213	
More cramps at 2 years	8/177	8/213	
More restless legs at 2 years	21/177	29/213	
Patient not satisfied – aesthetic at 2 years	23/177	31/213	
Patient not satisfied – functional at 2 years	17/177	17/213	
More pain at 1 year	14/188	20/221	
More tired/heavy feeling at 1 year	9/188	5/221	
More cramps at 1 year	9/188	10/221	
More restless legs at 1 year	26/188	34/221	
Patient not satisfied – aesthetic at 1 year	32/188	33/221	

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Interventi on</th><th>Comparis on</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="3">Patient not satisfied – functional at 1 year</td><td>28/188</td><td colspan="2">22/221</td><td colspan="3"></td></tr>
<tr><td colspan="3">More pain at 3 months</td><td>10/176</td><td colspan="2">12/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">More tired/heavy feeling at 3 months</td><td>2/176</td><td colspan="2">8/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">More cramps at 3 months</td><td>6/176</td><td colspan="2">9/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">More restless legs at 3 months</td><td>16/176</td><td colspan="2">27/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">Patient not satisfied – aesthetic at 3 months</td><td>19/176</td><td colspan="2">39/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">Patient not satisfied – functional at 3 months</td><td>15/176</td><td colspan="2">20/217</td><td colspan="3"></td></tr>
<tr><td colspan="3">Mean change of EQ-%D “health state” from baseline to 2 years</td><td>-1.8(25.4)</td><td colspan="2">-0.36(25.4)</td><td colspan="3">P=0.577 (no variances reported but common sd for each calculated as: 25.4)</td></tr>
<tr><td colspan="3">Complete satisfaction with reduction in venous complaints at 2 years</td><td>117/177</td><td colspan="2">127/213</td><td colspan="3"></td></tr>
<tr><td colspan="3">Need for >1 treatment</td><td>10/200
[2 for re-surgery, 8 for foam]</td><td colspan="2">40/230
[35 one extra session of foam, 5 >1 extra session]</td><td colspan="3"></td></tr>
<tr><td colspan="3">Adverse events (within 1 week)</td><td></td><td colspan="2"></td><td colspan="3"></td></tr>
<tr><td colspan="3">Groin infection</td><td>4/200</td><td colspan="2">0/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Haematoma</td><td>3/200</td><td colspan="2">0/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Parasthesia</td><td>6/200</td><td colspan="2">0/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Pain at injection site</td><td>0/200</td><td colspan="2">6/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Thrombophlebitis</td><td>0/200</td><td colspan="2">17/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Headache/migraine</td><td>0/200</td><td colspan="2">3/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">DVT</td><td>0/200</td><td colspan="2">1/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">PE</td><td>0/200</td><td colspan="2">1/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Later adverse events (at 2 yrs)</td><td></td><td colspan="2"></td><td colspan="3"></td></tr>
<tr><td colspan="3">Hyper-pigmentation</td><td>2/200</td><td colspan="2">12/230</td><td colspan="3"></td></tr>
<tr><td colspan="3">Telangiectatic matting</td><td>2/200</td><td colspan="2">6/230</td><td colspan="3"></td></tr>
</table>

Table 65: Wright2006[286]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Wright D, Gobin JP, Bradbury AW, Coleridge-Smith P, Spoelstra H, Berridge D, Wittens CHA, Sommer A, Nelzen O, and Chanter D. Varisolve 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 2006;21:180 – 190.</td>
<td>RCT, open-label, international, multicentre.
Randomisation not described. Allocation concealment unclear.
No blinding.</td>
<td>2 cohorts but only looking at the Varisolve cohort/ surgery (n=311); 210 patients randomised to Varisolve and 101 randomised to surgery.
Withdrew from study after treatment: 32 patients from Varisolve group and 7 from the</td>
<td>Inclusion: Male or female aged 18-75 years with moderate-to-severe varicose veins (C2-C4); SFJ or SPJ junction incompetence or both with retrograde blood flow for >1s and <7s demonstrated by duplex scanning; great saphenous incompetence and/or short saphenous incompetence; minimum of 10cm proximal trunk vein incompetence; normal deep venous system on duplex scanning, no evidence of occlusion or incompetence. Evidence of reflux was acceptable.
Exclusion: C5 and C6 excluded; history of major superficial thrombophlebitis; venographic or ultrasonographic evidence of current or previous DVT; immobility; BMI >32kg/m^2; contraindications for polidocanol including severe hypertension, diabetes, asthma and advance arteriosclerosis.
Baseline characteristics:
<table>
<tr><td></td><td>Surgery (n=94)</td><td>Varisolve foam sclerotherapy (n=178)</td></tr>
<tr><td>Mean age ±SD (years)</td><td>49±11.2</td><td>49.9±12.6</td></tr>
</table>
</td>
<td>N=94 patients treated with
Surgery: high ligation performed in 91.5% of patients, stripping in 88.3% and avulsion phlebectomy in 53.2%.</td>
<td>N=178 patients treated with
Varisolve$^{®}$ polidocanol microfoam; a uniform foam of physicologic gases, principally oxygen and carbon dioxide, combined with a 1% aqueous solution of polidocanol. Maximal dose initially set at 60mL and subseque</td>
<td>Days 7 and 28, and at months 3 and 12.</td>
<td>Post-procedure pain at Day 6 (Visual Analogue Scale (VAS) 1-100mm scale)
Response defined as: occlusion (or for surgery, absence) of the treated vein AND elimination of junctional reflux.
Adverse events: common treatment-related adverse events (i.e. contusion, skin</td>
<td>Acknowledgement of Sigvaris Ltd for the provision of compression stockings, but none declared for the provision of Varisolve.</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		surgery group.	M:F	34:60	66:112		ntly reduced to 30mL. The Varisolve technique carried out under ultrasound guidance. 30-40mmHg thigh length compression stocking worn 14 days post treatment.		discolouration, pain in limb, headache and haematoma) and serious adverse events (i.e. DVT, PE)	
			CEAP C3	11 (11.7%)	14 (7.9%)					
			CEAP C4	10 (10.6%)	20 (11.2%)					
			Primary VV							
			GSV	77 (81.9%)	141 (79.2%)					
			SSV	8 (8.5%)	12 (6.7%)					
			GSV+SSV	0	8 (4.5%)					
			Recurrent VV							
			GSV	6 (6.4%)	11 (6.2%)					
			SSV	2 (2.1%)	1 (0.6%)					
			GSV+SSV	1 (1.7%)	3 (1.7%)					

Results:

	Surgery (n=94)	**Varisolve foam sclerotherapy (n=178)**	p
Response (i.e. occlusion of trunk vein and elimination of reflux)			
at 3 months	82/94 (87.2%)	120/176 (68.2%)	
at 12 months	81/94 (86.2%)	111/176 (63.1%)	
Post-procedure pain at Day 6 (Median score on a	**9**	**2**	**<0.001**

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

100mm VAS scale)			
Most common treatment-related adverse events			
Contusion	80 (85.1%)	122 (68.5%)	-
Skin discolouration (= hyper pigmentation)	39 (41.5%)	98 (55.1%)	-
Pain in limb	39 (41.5%)	73 (41%)	-
Headache	20 (21.3%)	41 (23%)	-
Haematoma	1 (1.1%)	11 (6.2%)	-
Serious adverse events			
Deep vein thrombosis	0	9 (4.5%)	-
Pulmonary embolism	0	0	-

Author's conclusions: Varisolve was non-inferior to alternative treatment. Surgery was more efficacious, but Varisolve caused less pain. The Varisolve technique is a useful additional treatment for varicose veins and trunk vein incompetence.

G.5.2 Stripping surgery vs. endothermal ablation

Table 66: Carradice2011[47]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Carradice D, Mekako AI, Mazari FAK, Samuel N, Hatfield J and Chetter IC. Randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery 2011A; 98: 501-510.</td>
<td>RCT. Non blinded. “Randomisation” through choice of sealed envelopes by the patient. This method, though unorthodox, ensures allocation concealment provided all envelopes are identical and have been properly shuffled. However, towards the end of the trial, it may become easier to guess to which group recruited subject will be allocated, if it is known that there has</td>
<td>280 randomised (140 from each group). In endovenous laser ablation (EVLA) group, 1 did not receive intervention; in surgery group, 3 did not receive intervention (all withdrew from trial). Over one year, in EVLA group 24 lost to follow-up and in surgery group 15 lost to</td>
<td>Inclusion: patients with primary symptomatic unilateral varicose veins, with isolated SFJ incompetence, and reflux in the GSV. Incompetence defined as reflux of at least 1 sec on Doppler.

Exclusion: previous treatment for ipsilateral varicose veins, deep vein incompetence or obstruction, age < 18 years, pregnancy, impalpable foot pulses.

Baseline characteristics: Only significant difference was for SF36 mental health (p=0.03). Continuous vars all mean (sd) unless stated. * median (IQR)
<table>
<tr><th></th><th>EVLA</th><th>Surgery</th></tr>
<tr><td>Age</td><td>49 (14)</td><td>49 (13)</td></tr>
<tr><td>M:F</td><td>54:85</td><td>47:90</td></tr>
<tr><td>ex smoker</td><td>35/132</td><td>37/130</td></tr>
</table>
</td>
<td>Stripping surgery. Flush SFJ ligation followed by ligation of all tributaries to the 2nd branch, then inversion stripping of the GSV to the knee. GA used.

Common procedures: Multi-phlebectomies given to both groups as needed.</td>
<td>EVLA. GSV cannulated at the lowest point of reflux. EVLA at 810nm wavelength and power 14W applied during withdrawal. LA used.</td>
<td>1 week, 6 weeks, 3 months and 1 year.</td>
<td>SF-36
EuroQoL 5D
AVVQ
CEAP
VCSS
post-op pain
Satisfaction with cosmetic result.</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	been an imbalance of allocations up to that point. In that sense, the risk of allocation concealment breaking down is possible.	follow-up.	current smoker	35/132	30/130					
			BMI	26.6 (5.0)	26.0 (4.3)					
			GSV diam (groin) mm	8.7 (2.7)	8.2 (2.7)					
			VCSS*	4 (3-5)	4 (3-5)					
			CEAP 2	95/138	96/137					
			CEAP 3-6	43/138	41/137					
			AVVQ*	12.6 (9.6-17.2)	13.7 (9.9-18.2)					
			SF36*							
			physical functioning	90 (75-100)	90 (80-100)					
			role physical	100 (50-100)	100 (75-100)					
			bodily pain	74 (52-100)	74 (52-100)					
			gen health	77 (62-92)	77 (67-87)					
			Vitality	70 (55-80)	70 (53-80)					
			social functioning	100 (75-100)						
			role emotional	100	100					
			mental	84 (68-	80 (68-90)					

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			health	92)						
			EQ5d*	0.848 (0.796-1.00)	0.841 (0.796-1)					
			SF6D*	0.804 (0.744-0.856)	0.795 (0.717-0.847)					

Results:

	EVLA	Surgery	p
Health related QoL (SF36) Higher score is better outcome). Median (IQR)			
physical functioning -1week	88 (70-95)	80(65-90)	0.012
role physical -1week	100 (25-100)	50(0-100)	0.005
bodily pain -1week	74(54-84)	62(41-74)	0.031
gen health -1week	81(67-92)	82(72-92)	NS
vitality -1week	70(60-80)	65(55-800	0.049
social functioning -1week	100 (75-100)	75(63-100)	0.004
role emotional -1week	100	100(67-100)	0.027
mental health -1week	88(76-92)	84(68-92)	NS
physical functioning -1year	95(85-100)	95(80-100)	
role physical -1year	100	100	NS
bodily pain -1year	100(72-100)	94(72-100)	NS
gen health -1year	82(67-92)	82(72-92)	NS
vitality -1year	75(60-85)	75(65-85)	NS
social functioning -1year	100(88-100)	100(75-100)	NS
role emotional -1year	100	100	NS
mental health -1year	88(74-92)	88(76-92)	NS
AVVQ 1 week	16.6 (12.4-21.1)	16.5(12.2-22.7)	NS
AVVQ 1 year	2.0(0-5.3)	2.0(0-5.3)	NS

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
EQ5D - 1 week			0.796(0.760-1)	0.801(0.691-0.895)	NS			
EQ5D – 1 year			1(0.877-1)	1(0.841-1)	NS			
SF-5D – 1 week			0.796(0.735-0.838)	0.759(0.672-0.830)	0.003			
SF-5D – 1 year			0.843(0.773-0.876)	0.835(0.777-0.878)	NS			
pain at day 1			less pain from day 1 to day 6 in EVLA gp (p=0.004 to <0.001). But no data given except in low resolution figure.					
VCSS at 1 year			1(0-1)	1(0-1)	**NS**			
Adverse events								
sensory disturbance			4/137	13/133	0.020			
haematoma			1/137	11/133	0.003			
infection			2/137	8/133	0.048			
phlebitis			4/137	6/133	0.536			
persistent pain			1/137	5/133	0.116			
pigmentation			4/137	1/133	0.371			
anaesthetic complication			0/137	3/133	0.118			
persistent bruising			1/137	2/133	0.618			
allergy			0/137	1/133	0.493			
thromboembolism			0/137	0/133	1			
Cosmetic satisfaction at 1 year			EVLA higher satisfaction (p=0.034) but no data given.					
Overall satisfaction at 1 year			No difference between groups for overall satisfaction (NS) but no data given in paper.					

1

Table 67: Carradice2011A[48]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Carradice D, Mekako AI, Mazari FAK, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery 2011; 98: 1117-1123.	This is the same study as Carradice 2011A, with some additional outcomes. See Carradice 20011A	None	Carradice D, Mekako AI, Mazari FAK, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery 2011; 98: 1117-1123.	This is the same study as Carradice 2011A, with some additional outcomes. See Carradice 20011A	None	Carradice D, Mekako AI, Mazari FAK, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery 2011; 98: 1117-	This is the same study as Carradice 2011A, with some additional outcomes. See Carradice 20011A	None

Reference	**Study type**	**No. of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
						1123.		

Results			
	Surgery	**EVLA**	**p**
Initial treatment failure [defined as failure to fully remove the GSV and all groin SFJ tributaries (Surgery), or flow in competent GSV (EVLA)] – data collected within 6 weeks	10/132	1/137	0.005
Clinical recurrence after 1 year (defined as the development of neovascularisation (Surgery) or recanalisation (EVLA), or the development of new segments of incompetence in superficial veins and perforators.	23/113	5/124	0.001

Table 68: Darwood2008[67]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Darwood RJ, Theivacumar N, Dellagrammaticas D, Mavor AID, Gough MJ. Randomised clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. British Journal of Surgery 2008; 95: 294-301</td>
<td>RCT, UK.

Allocation concealment likely through the use of sealed envelopes. Randomisation method unclear.

No ITT used.

Drop out:

EVLA1:3/49 legs

EVLA2: 9/42 legs

SURGERY: 11/45 legs

Reasons: unclear</td>
<td>136 legs from 118 patients – if bilateral symptoms, both legs were used in the study, and each leg was given the same treatment. This will have artificially reduced variance within groups, but as data were analysed non-parametrically this will not have mattered.</td>
<td>Inclusion: >18 years with symptomatic varicose veins and primary saphenofemoral incompetence confirmed with duplex US.

Exclusion: taking warfarin, or patient unsuitable for EVLA (twisted GSV, large incompetent anterior accessory saphenous vein) or surgery (co-morbidity prohibiting general anaesthesia).

Baseline characteristics: Medians and IQR shown. No statistical testing as sample size calculation target not met (very sensible as lack of power would lead to over-confidence in group equivalence).
<table>
<tr><th></th><th>EVLA1</th><th>EVLA2</th></tr>
<tr><td>Age</td><td>42 (30.5-54.5)</td><td>52 935-59)</td></tr>
<tr><td>F:M ratio</td><td>22:16</td><td>16:11</td></tr>
<tr><td>CEAP2</td><td>37/47</td><td>24/33</td></tr>
<tr><td>CEAP3</td><td>4/47</td><td>6/33</td></tr>
<tr><td>CEAP4</td><td>2/47</td><td>1/33</td></tr>
</table>
</td>
<td>Saphenofemoral ligation, GSV stripping to knee level with perforation invagination stripper, and multiple phlebectomies of varicosities as a day case under GA.

Prophylactic heparin given pre-surgery. LA applied to the wound area but not the GSV tract.

Non stretch bandaging used for 1 day, followed by full length grade II compression stocking for 2 weeks.</td>
<td>Endovenous laser ablation (EVLA) using a 810nm diode laser source. The GSV was cannulated near the knee under US-guidance and LA applied to the vein. A 600 micron laser fibre inserted and drawn back through the vein.

Two different laser protocols were used:

EVLA1: 12W power with 1 sec pulses and 1 sec intervals. Catheter withdrawn 2-3 mm on each</td>
<td>1, 6, 12 and 52 weeks post treatment.</td>
<td>Disease specific QoL [Aberdeen VV symptom score (AVVSS)]

Abolition of reflux with Duplex imaging

Patient symptoms and cosmesis

Patient satisfaction</td>
<td>not stated</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Loss to follow-up (none of those dropping out were followed up): EVLA1:5/46 legs EVLA2: 4/33 legs SURGERY: 2/34 legs Reasons unclear		CEAP5	3/47	0/33		rest interval. EVLA2: 14W power continuously with constant 2-3 mm/sec withdrawal. Non stretch compression bandage applied postoperatively for 1 week, followed by a grade II compression stocking for a further week. **Injection sclerotherapy would be performed at 6 weeks for residual varicosities if requested by the patient.** This partially controls for the		Physician outcomes – venous clinical severity score (VCSS) Adverse events, including post-procedure pain.	
			CEAP unknown	1/47	2/33					
			VCSS	4 (3-5)	4 (3-5)					
			bilateral	9/47	6/33					
			AVVSS	11.76 (9.8-19.4)	14.3 (8.9-19.6)					

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					phlebectomies given to the surgery group, but there is still a possibility that the differences between sclerotherapy and phlebectomies would have confounded results.			

Results: Median (IQR)				
Outcome	**EVLA1**	**EVLA2**	**Surgery**	**p**
QoL – AVVSS 3months (score out of 100, with 100 worst symptoms?)	5.6 (1.45-8.2); n=34	4.2 (1.7-7.9); n=20	5.32 (1.0-7.7); n=26	not stated
QoL – AVVSS 12months	1.8 (0.1-5.9); n=22	2.5 (0-5.6); n=15	3.9 (0-10.3); n=9	not stated
QoL – AVVSS improvement from baseline at 3months	9.4 (4.5-14.9)	10.3(5.0-15.0)	8.4 (4.5-13.2)	0.694
Abolition of GSV reflux at 12 weeks	41/42	26/29	28/32	0.227
Abolition of GSV reflux at 52 weeks (includes only those with abolition at 12 weeks)	24/28	19/21	11/12	
Abolition of SFJ reflux at 12 weeks	39/42	27/29	32/32	0.307
Abolition of SFJ reflux at 52 weeks (includes only those with abolition at 12 weeks)	23/28	19/21	11/12	
VCSS	0 (0-1)	0 (0-1)	0 (0-1)	NS

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Patient satisfaction at 12 weeks (100mm VAS; 100 = high satisfaction)	95 (81-95)	91 (84-97)	91 (81-95)	0.267
Cosmesis at 12 weeks (100mm VAS; 100 = high satisfaction)	92 (80-95)	92 (77-95)	93 (76-98)	0.980
Adverse events	**EVLA1**	**EVLA2**	**Surgery**	
Post-operative pain (mean of the first 7 days medians	11	18	14	
symptomatic phlebitis	6/42	3/29	0	
paraesthesiae/ numbness	0	1/29	4/32	
pruritis at cannulation site	0	1/29	0	
upper thigh discolouration/bruising	0	1/29	2/32	
wound infections requiring antibiotics	0	0	2/32	
ARDS, leading to 7 days ventilation in ICU	0	0	1/32	
Treatment failure	see abolition of reflux results			
return to work in one week	29/34	20/24	14/25	

Table 69: Elkaffas 2011[113]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>ElKaffas KH, ElKashef O, ElBaz W. Great Saphenous Vein Radiofrequency Ablation versus standard dtripping in the management of primary varicose veins – a randomised clinical trial. Angiology 2011; 62: 49-54</td>
<td>RCT. Randomisation method was where patients “blindly choose an assignment card that would put them in either group”: this has clear scope for unconscious bias from the researcher. For example, the card relating to the preferred allocation could be placed in a certain position aimed at encouraging its choice. Allocation</td>
<td>180 patients. 90 in EVRF group and 90 in surgery group. Drop out data is unclear, as 90 are reported to have had treatment in the EVRF group, but the drop-out data for that group are reported with a denominator of 88. Drop-outs over 24 months were 7 for the EVRF group and 9 for the surgery group. No ITT</td>
<td>Inclusion: SFJ and GSV reflux on duplex, either on standing manual compression/release or Valsalver manoeuvres.

Exclusion: Patients with deep or superficial venous thrombosis; patients on anticoagulants; PAD, pacemakers, serious systemic disease, pregnancy. Also GSV lumen diameter > 18mm in the thigh or very twisted veins.

Baseline characteristics: surgery group older and with larger GSV diameter. All else not significant.
<table>
<tr><th></th><th>EVLA</th><th>Surgery</th></tr>
<tr><td>Age</td><td>33.1 (2.6)</td><td>34.9 (3.7)</td></tr>
<tr><td>M:F</td><td>42:48</td><td>45:45</td></tr>
<tr><td>discomfort</td><td>69/90</td><td>66/90</td></tr>
<tr><td>oedema</td><td>36/90</td><td>42/90</td></tr>
<tr><td>skin changes</td><td>12/90</td><td>18/90</td></tr>
<tr><td>C2</td><td>51</td><td>45</td></tr>
</table>
</td>
<td>SF high ligation and GSV stripping at ankle (n=40) or knee (n=50). GA used for all, all were managed as inpatients. Stripping performed after wrapping elastic bandage to reduce postoperative haematoma, with operating table tilted 30 deg foot up.

Common procedures: Both groups had stab phlebectomies as needed (15/90 in EVRF gp and 39./90 in</td>
<td>Radiofrequency ablation (EVRF) used. Closure system (VNUS medical technologies) used. two operators involved. Vein cannulated at point of most distal reflux and tip of RF catheter placed at least 2cm distal to the saphenofemoral junction or just distal to the superficial epigastric vein orifice. LA used only. RF catheter used temperatures of 80-85 deg. One operator only.</td>
<td>1 week, 1 month, 6 months, 12 months 18 months, 24 months. Mean FOLLOW-UP 20.9 (6.8) months.</td>
<td>Treatment failure

Adverse events

Recurrence</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	concealment is inherent in the design, as the allocation cannot be known by the researcher until it is made by the patient; however the problems with unconscious bias remain. No evidence of blinding.	(imputation) was reported. This would only be relevant to the Kaplan Meir analysis, which will hopefully have censored the data.	C3	27	27	surgery group).	**24/90 also needed later postoperative sclerotherapy for small veins was needed (none in surgery group).**			
			C4	9	12					
			C5	3	6					
			GSV diameter (mm) [mean(range)]	7.8 (4.5-12)	8.6 (4-14)					
			op duration (mins)	40 (12)	45 (13)					

Results:

	EVLA	Surgery	p
Treatment failure at completion of intervention (no full occlusion or failure to remove the GSV)	6/90	0/90	
Adverse events (imm. Post op)			
focal paresthesia	9/90	3/90	
Thrombophlebitis	6/90	0/90	
severe pain requiring analgesics	12/90	12/90	
hematoma formation	1/90	12/90	
iliofemoral DVT	0/90	1/90	
severe groin infection	0/90	3/90	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

pulmonary embolism	0/90	0/90	
Recurrence over 24 months	12/90	9/90	
Average (?median) time to recurrence (Kaplan Meier graph provided but no data given)	23.3 months (95%CI: 22.5-24.1)	23.0 months (95%CI: 21.3-24.6)	**0.4**
return to normal activity	3 (3)	7 (2.6)	

Table 70: Flessenkamper 2012[99]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Flessenkamper I, Hartmann M, Stenger D, Roll S. Endovenous laser ablation with and without high ligation compared with high ligation and stripping in the treatment of great saphenous varicose veins: initial results of a multicentre randomised controlled trial. Phlebology 2012; DOI: 10.1258/phleb.2011.011147</td><td>RCT. Three arm RCT, but one arm not included in this review (EVLA with high ligation) as it is not “standard” treatment. Non computer randomisation but clear allocation concealment. No assessor or other blinding.</td><td>301 randomised to the 2 arms under consideration. No attrition at 2 months follow-up</td><td>Inclusion: 18-72 years; clinical signs or symptoms of superficial venous insufficiency with proven reflux into GSV; life expectancy > 5 years;
Exclusion: previous surgery of the GSV.
All had insufficient terminal valve, diameter of the GSV 5cm distal from the junction was ≤16mm.
Baseline characteristics: Groups very comparable:
<table>
<tr><th></th><th>Strip</th><th>EVLA</th></tr>
<tr><td>age</td><td>47.7(11.5)</td><td>47.7(12.9)</td></tr>
<tr><td>%male</td><td>29.8%</td><td>31.7%</td></tr>
<tr><td>Hach stages</td><td></td><td></td></tr>
<tr><td>II</td><td>5.1%</td><td>7.1%</td></tr>
<tr><td>III</td><td>51.3%</td><td>51.4%</td></tr>
<tr><td>IV</td><td>43.7%</td><td>41.4%</td></tr>
<tr><td>No pre-op pain</td><td>62.4%</td><td>51.8%</td></tr>
<tr><td>Localised lipodermatosis</td><td>11.3%</td><td>7.2%</td></tr>
</table></td><td>High ligation of the SFJ and stripping using invagination technique. Open surgery. Anaesthetic unclear. Miniophlebectomies carried out as required</td><td>980nm laser (EVLA) at 30W in continuous mode. Performed under duplex guidance. Tumescent anaesthesia. Miniophlebectomies carried out as required.</td><td>2 months</td><td>AEs
GSV reflux</td><td>German society of phlebology</td></tr>
<tr><td colspan="9">Results:</td></tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Stripping	**EVLA**	**p**
Adverse Events			
DVT	1/159	1/142	
Lymphoedema	4/159	2/142	
Neurological sensory deficits	2/159	3/142	
Ecchymosis	100/159	72/142	
Post op pain day 1	6/159	4/142	
Post op pain 2-5 days	23/159	20/142	
Post op pain >5 days	50/159	57/142	
Saphenous nerve damage	1/159	5/142	
SFJ reflux at 2 months	0/159	38/142	P<0.0001
Work disability (days)	9.2	9.3	
VDS - asymptomatic	77/159	84/142	

1

Table 71: Hinchcliffe 2006[114]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hinchliffe RJ, Ubhi J, Beech A, Ellison J, Brathwaite BD. A prospective randomised controlled trial of VNUS Closure versus surgery for the treatment of recurrent long saphenous varicose veins. Eur J Vasc Endovasc Surg. 2006; 31: 212-218.	Randomised **within-subject** design. The researchers used a non-specified random method to decide which side was treated with what. Allocation concealment not applicable, as the decision on the side would be made after the recruitment. Patients reported to be blinded as to the treatments used on each side, assisted by the use of opaque dressings over the groin. Assessor photographing patients' legs for assessment of bruising was blinded to	16 patients. No reports of loss to follow-up.	**Inclusion**: recurrent varicose veins previously treated by sapheno-femoral ligation; all CEAP 2 and above; persistent and incompetent GSV suitable for treatment with EVRF; >18 yrs; **Exclusion:** pregnancy, twisted GSV, GSV <3mm, > 12mm; thrombotic scarring of GSV; no GSV present. **Baseline Characteristics:** 12 women, 4 men; median age 54 (44-66 yrs); median CEAP: 3 (class 2, n=1, class 2, n=14, class 4, n=1).	Ligation and inversion stripping to just below the knee. to just below the knee. **Common procedures**: Multiple stab avulsions, general anaesthetic, compression bandages for 2 weeks.	EVRF with VNUS closure system. The probe was retracted in 1cm increments.	6 weeks, 1 year		None

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	patient group.							

Results: No variances given for continuous variables.

	Surgery	EVLA	p
Post Ix pain (time point not given) [VAS]; median (IQR)	3.8 (0.6-6.3)	1.7 (0.2-4)	0.02
Post Ix bruising (time point not given) [VAS]; median (IQR)	5.2 (2.6-7.0)	1.7 (0.4-4.4)	0.03
% of bruising covering legs (time point not given); median (IQR)	21.8 (15.7-28.5)	11.9 (8.9-18.3)	0.02
Adverse events DVT vessel perforation PE skin burns lymphatic leak post operative neuralgia thigh discomfort wound infection numbness thrombophlebitis leg oedema	 0/16 0/16 0/16 0/16 0/16 0/16 0/16 1/16 3/16 1/16 1/16	 0/16 0/16 0/16 0/16 0/16 2/16 2/16 0/16 0/16 0/16 0/16	
non-fully stripped / non- occlusion 6 weeks	2/16	3/16	
persistent incompetence in accessory truncal veins 6 weeks	2/16	3/16	

Table 72: Lurie2003[152]

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, Schuller-Petrovic S, Sessa C. Prospective randomised study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS study). J Vasc Surg 2003; 38: 207-14	RCT. Multi-site in 3 countries: 2 sites in USA, 2 in France and 1 in Austria. Each site had performed at least 15 EVLs as well as “previous experience” in the Stripping and ligation surgery methods. Randomisation unclear: “via internet”. Allocation concealment unclear. Blinding unclear. Bilat treatment of one patient in the EVRF	85 patients (86 limbs) used. 45 (46limbs) allocated to the EVRF group and 40 to the surgery group. 3 patients immediately withdrew after discovering they were in the surgery group. A further surgery pt did not receive treatment due to non-attendance. One	Symptomatic varicose veins and GSV incompetence, confirmed with duplex. **Inclusion:** Reverse flow lasting .0.5 secs in standing; age 21-80 yrs; C2-4 classification; ambulatory; saphenous vein $\leq$ 1.2 cm in supine; segmental deep reflux permissible. **Exclusion:** vein diameter >1.2 cm or <0.2 cm. Duplication of saphenous trunk or incompetent accessory saphenous branch; small SV reflux; thigh varices; prev. DVT; ABI<0.9; axial DV reflux; twisted GSV segment to be treated. **Baseline characteristics:**			Physicians followed their standard practice using either an olive-tipped device or a PIN stripper. Ligation in the femoral triangle. **Common procedures**: Adjunctrive procedure on varices and perforator vessels limited to below-knee.	EV radio-frequency obliteration. The Closure catheter and system (VNUS med technologies) was used according to established methods.	72 hours, 1 wk, 3 wks, and 4 months.	Disease specific QoL Occlusion and reflex rates patient reported symptoms Adverse events	VNUS medical technologies, inc. Clear conflict of interest.
				EVRF	surgery					
			Age	49 (4)	47 (4)					
			VCSS	4.8 (0.34)	4.39 (0.38)					
			Female	32 (74.4)	26 (72.2)					
			Working	25/44	25/36					
			CEAP2	36/44	28/36					

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	group, thus artificially decreasing variance in that group.	EVRF patient was withdrawn after discovery of previous surgery in the same vein. One further EVRF patient was withdrawn from follow-up after he was found to have C6, a protocol violation.	CEAP4	4/44	4/36					
			GA used	12/44	19/44					
			Adjunctive phlebectomies done	42/44	36/36					
			mean avulsions/extremity	8.6 (2.6)	9.8 (2.8)					
			mean length of treated segment (cm)	37 (2)	40 (2)					
			site 1	20	14					
			site 2	6	9					
			site 3	7	7					
			site 4	9	3					
			site 5	2	3					

Results: Comparisons of QoL scores were adjusted for the type of anaesthesia and number of adjunctive procedures.

	EVRF	**Surgery**
CIVIQ2 Disease specific QoL (0-100, 100 worst) global score (mean (**se**)). Change from baseline to 72 hrs.	-3 (2.7)	13.3 (3.1)
CIVIQ2 Disease specific QoL (0-100, 100 worst) global score (mean (**se**)). Change from baseline to 1 wk	-9.2 (2.3)	3.7 (2.5)
CIVIQ2 Disease specific QoL (0-100, 100 worst) pain dimension	-1.77 (0.6)	2.9 (0.7)

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
(mean (**se**)). Change from baseline to 72 hrs								
CIVIQ2 Disease specific QoL (0-100, 100 worst) pain dimension (mean (**se**)). Change from baseline to 1 wk			-2.4 (0.6)			1.2 (0.7)		
CIVIQ2 Disease specific QoL (0-100, 100 worst) physical score dimension (mean (**se**)). Change from baseline to 72 hrs			0.82 (0.69)			4.85 (0.79)		
CIVIQ2 Disease specific QoL (0-100, 100 worst) physical score dimension (mean (**se**)). Change from baseline to 1 wks			-0.97 (0.65)			2.02 (0.72)		
NB: The other two dimensions of the CIVIQ2 are not reported except the fact that they were NS. Data at later follow-ups not reported!								
Occlusion and reflux rates								
reflux at 72 hrs			5/43			0/36		
reflux at 1 week			unclear			0/36		
complete occlusion of GSV at 72 hours			36/43			0/36		
complete occlusion of GSV at 1 wk			41/43			0/36		
complete occlusion of GSV at 3 wks			41/43			0/36		
complete occlusion of GSV at 4 months			42/43			0/36		
patient reported symptoms			No reporting in any detail, except that EVRF showed a clear advantage for "pain". The VCSS is mentioned vaguely but no reports of any data except at baseline.					
Adverse events at 72 hrs								
none			19/44			6/36		
infection			0/44			2/36		
superficial venous thrombosis			0/44			1/36		
tenderness			2/44			9/36		
lymphocele			0/44			0/36		
bleeding from stab wound			3/44			3/36		
eccymosis			12/44			19/36		
erythema			6/44			3/36		
hematoma			7/44			14/36		

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
paresthesia			5/44			2/36		
hyper pigmentation			0/44			0/36		
Adverse events at 1 week								
none			15/44			5/36		
infection			0/44			1/36		
superficial venous thrombosis			1/44			2/36		
tenderness			5/44			10/36		
lymphocele			0/44			1/36		
bleeding from stab wound			0/44			0/36		
eccymosis			14/44			23/36		
erythema			2/44			1/36		
hematoma			6/44			18/36		
paresthesia			10/44			5/36		
hyper pigmentation			0/44			0/36		
Adverse events at 3 weeks								
none			31/44			14/36		
infection			0/44			1/36		
superficial venous thrombosis			2/44			1/36		
tenderness			4/44			9/36		
lymphocele			0/44			0/36		
bleeding from stab wound			0/44			0/36		
eccymosis			1/44			7/36		
erythema			1/44			3/36		
hematoma			1/44			12/36		
paresthesia			7/44			2/36		
hyper pigmentation			1/44			0/36		

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse events at 4 months								
none			36/43			26/34		
ecchymosis			0/43			1/34		
erythema			0/43			2/34		
hematoma			0/43			3/34		
Treatment failure			2/44			0/36		
return to normal activity			1.15 (1.5)			3.89 (1.5) 0.02 (sds calculated from the p value and MD)		

Table 73: Lurie2005[153]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, Sessa C and Schuller-Petrovic S. Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): Two-year follow-up. Eur J Vasc Surg 2005; 29, 67-73	RCT. Follow up to Lurie 2003. Please see table for Lurie 2003.	As Lurie 2003. This study involved follow-up at 2 further time points: 1 year and 2 years. At one year, data were missing for 21 limbs in the EVLA group and 20 limbs from the surgery group. At 2 years, data were missing for 10 limbs in the EVLA group and 11 limbs from the surgery	See Lurie 2003. In addition CEAP scores at baseline were reported as equivalent, with 82% and 78% at C2 in EVLA and surgery respectively, 9% and 11% at C3 and 9% and 11% at C4 (chi sq. 0.2, P=0.9).	see Lurie 2003	see Lurie 2003	As Lurie 2003, plus 1 year and 2 years.	Some outcomes missing from the Lurie 2003 paper are included in this, as well as new 1 yr and 2 year data. QoL Reflux rates Recurrence rates VCSS	not stated

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		group.						

Results:

	EVRF	Surgery					
reflux at 4 months reflux at 2 years	4/43 2/36	 3/29					
Cumulative rates of recurrent varicose veins at combined 1 and 2 years follow-up	14.3%	20.9%	long rank test NS				

CIVIQ2 Disease specific global QoL at 1 year and 2 years	Data only shown in figure (low resolution of figure and ambiguity about whether variance is sd or SE makes data extraction impossible). However reported that the EVLA group had a significantly lower (better) QoL at 1 year and at 2 years.
CIVIQ2 Disease specific pain dimension of QoL at all time points	Data only shown in figure (low resolution of figure and no variance indicators makes data extraction impossible). However reported that the EVLA group had a significantly higher improvement in pain score (from baseline values) at all time points from 72 hrs to 2 years.
VCSS	Data only shown in figure (low resolution of figure and ambiguity about whether variance is sd or SE makes data extraction impossible). However reported that the EVLA group had a significantly lower (better) VCSS at 72 hrs and 1 week (this was unreported in earlier report) but not significantly different at other time points

	EVRF		Surgery	
		%		%
CEAP scores at 4 mths (analysed categorically with a chi square analysis)	C0	34.1	C0	41.2

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	C1	38.6	C1	32.4
	C2	18.2	C2	20.6
	C3	0	C3	2.9
	C4	9.1	C4	2.9
		%		%
CEAP scores at 1 yr (analysed categorically with a chi square analysis)	C0	28	C0	15
	C1	56	C1	40
	C2	8	C2	30
	C3	0	C3	5
	C4	8	C4	10
		%		%
CEAP scores at 2 yrs (analysed categorically with a chi square analysis)	C0	33.3	C0	27.6
	C1	41.7	C1	31
	C2	22.2	C2	31
	C3	0	C3	3.4
	C4	2.8	C4	6.9
Treatment failure	See Lurie 2003			

Table 74: Perala2005 [204]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Perala J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T, Juvonen T. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3 year outcome of a randomised study. Ann Vasc Surg 2005; 19: 669-672.	3 year follow-up of Rautio 2002.	see Rautio 2002. No further drop out from 50 days to 3 years.	See Rautio 2002	Stripping surgery. Groin dissected to expose the SFJ. Side branches of the GSV at the SFJ were divided and ligated. After local phlebectomy, the GSV was stripped from just below the knee to the groin with the venostrip with a 9mm olive.	Radiofrequency endovenous obliteration carried out with the VNUS Closure system (see Lurie studies).	3 years.	Decrease in VCSS VDS at 3 years VSDS at 3 years Satisfaction with cosmetic result. Recurrence Treatment failure	not stated

Results:

	EVRF	Surgery	p
Average decrease in VCSS from baseline to 3 years [mean(sd)]	4.3 (2.3)	4.0 (1.2)	0.7
VDS at 3 years (median (range))	0 in all except for 1	0 in all except for 1	1
VSDS at 3 years	0 in all except for 3	0 in all except for 1	**0.6**
Lack of satisfaction with cosmetic result at 3 years	1/15	2/13	
Would not recommend to a friend	0/15	0/13	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Recurrence of varicose veins as determined by surgeon	5/15	2/13	0.4??
Recurrence of varicose veins as determined by patient	4/15	2/13	0.065??
Reoperation for recurrent varicose veins	1/15	1/13	
Adverse events symptom relating to saphenous nerve injury superficial thrombophlebitis	 1/15 1/15	 5/15 0/15	
Treatment failure	see Rautio 2002		
Reflux	3/15	0/15	

1 **Table 75: Pronk2010**[213]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Pronk P, Gauw SA, Mooij MC, Gaastra MTW, Lawson JA, van Goethem AR, van Vlijmen-van Keulen CJ. Randomised controlled trial comparing saphenofemoral ligation and stripping of the great saphenous vein with endovenous laser ablation (980nm) using local tumescent anaesthesia: one year results. Eur J Endovasc Surg 2010; 40: 649-656.</td>
<td>RCT. Non blinded. Computer randomisation used. No reporting of allocation concealment.</td>
<td>130 legs in 122 patients (EVLA n=62; surgery n=68). Patients with bilateral VV were randomised only once. All had treatment.
At 6 weeks, 2 lost to follow-up from surgery group, none from the EVLA group. The 2 lost to follow-up did complete their post-op questionnaires. There was further loss to follow-up at 1 year (7 further lost in surgery group and 6 further lost in the EVLA group)</td>
<td>All GP referrals with primary varicose veins.
Inclusion: >18 years; CEAP ≥ 2; Reflux >0.5 secs on duplex; GSV diameter between 0.3 and 1.5cm.
Exclusion: Previous surgery of the GSV; intrafascial GSV reflux length <15cm measured from SFJ downwards; pregnancy; immobility; intolerance of lidocaine; active superficial phlebitis; previous or deep VT; deep venous insufficiency.
Baseline Characteristics:
<table>
<tr><th></th><th>Surgery (n=68)</th><th>EVLA (n=62)</th></tr>
<tr><td>M:F</td><td>15:53</td><td>16:46</td></tr>
<tr><td>Age</td><td>50(10.5)</td><td>49(11)</td></tr>
<tr><td>BMI</td><td>24.5(3.7)</td><td>25(3.3)</td></tr>
<tr><td>Diam GSV</td><td>0.64(0.14)</td><td>0.64(0.16)</td></tr>
<tr><td>tired legs</td><td>35/68</td><td>31/62</td></tr>
<tr><td>oedema</td><td>32/68</td><td>21/62</td></tr>
</table>
</td>
<td>High ligation of GSV and ligation of all tributaries via groin incision, followed by PIN stripping, with access via incision below the knee.
Common procedures: Tumescent anaesthesia given to all. Sclerotherapy of superficial varicose veins also given to all. Short stretch bandages applied to the whole leg for 1 week.</td>
<td>EVLA. Proximal 10cm of the incompetent GSV treated with an energy does of 100 J/min followed by a targeted energy dose determined by the diameter of the GSV (0.3-0.4 – 50 J/cm up to >0.6 cm – 80 J/cm).</td>
<td>1 week, 6 weeks, 6 months, 12 months.</td>
<td>Post op pain
Symptoms
CEAP score
Patient satisfaction</td>
<td>None</td>
</tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			itching	26/68	20/62					
			cosmetic	13/68	13/62					
			pain	13/68	9/62					
			restless legs	6/68	11/62					
			calf cramps	8/68	8/62					
			CEAP 2	26/68	29/62					
			CEAP3	36/68	29/62					
			CEAP4	5/68	4/62					
			CEAP5	1/68	0/62					

Results:

	Surgery	EVLA	P
Post-op pain during op	3.39(2.57)	2.21(2.40)	
Post-op pain day1	4.00(2.34)	3.58(2.600	
Post-op pain day2	3.12(2.38)	3.05(2.48)	
Post-op pain day3	2.38(2.11)	2.76(2.53)	
Post-op pain day7	1.78(1.94)	3.74(2.72)	
Post-op pain day10	1.18(1.49)	2.65(2.21)	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Post-op pain day14	0.77(1.46)	1.66(2.04)	
Tired legs 1 year	8/62	5/56	0.49
oedema 1 year	10/62	6/56	0.39
itching 1 year	6/62	3/56	0.50
cosmetic 1 year	8/62	4/56	0.31
pain 1 year	6/62	1/56	0.12
restless legs 1 year	4/62	7/56	0.43
calf cramps 1 year	2/62	5/56	0.25
CEAP 0 1 year	21/61	19/56	0.96
CEAP 1 1 year	22/61	20/56	0.97
CEAP 2 1 year	11/61	9/56	0.78
CEAP 3 1 year	6/61	7/56	0.65
CEAP 4 1 year	0/61	1/56	
CEAP 5 1 year	1/61	0/56	
QoL – cosmetic concerns (VAS) at 6 months [10 best]	7 (4-10)	7.5 (3-10)	
Willing to do the same procedure again	53/67	47/61	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Would recommend to a friend or relative		59/67	51/61					
Adverse events								
wound infection		0/67	0/61					
DVT		0/67	0/61					
post op bleeding		2/67	0/61					
Thrombus at SFJ		0/67	3/61					
paresthesia		1/67	2/61					
persistent neurological injury (1 year)		1/67	0/61					
Recurrence at 1 year (presence of reflux)		5/56	5/49					
Recanalisation of GSV			3/49					
return to normal activities		3.2 (4)	3.2 (4.3)					

Table 76: Rasmussen2007[219]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rasmussen LH, Bjoern L, Lawaetz M, Blemings A, Lawaetz B, Ekolof B. Randomised trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short term results. J Vasc Surgery 2007; 46: 308-15	RCT. Randomisation method unclear, but blocks of 10 were used. Allocation concealment achieved through sealed envelopes. Two experienced surgeons involved, but unclear whether these did both or just one kind of intervention. Two centres also involved, but unclear how these were distributed across groups. Bilateral treatment allowed, with	121 patients (137 legs). ITT reported as used, but unclear about how the loss to follow-up were managed. No evidence of data imputation. Loss to follow-up (cumulative):	**Inclusion:** varicose veins, CEAP C2-4 EpAsPr. Aged 18-80 yrs. GSV incompetence defined by reflux >0.5 sec on duplex. Previous high ligation was permitted. **Exclusion:** Duplication of the saphenous trunk, incompetent anterior accessory GSV, previous DVT, arterial insufficiency and/or ankle-brachial index <0.9, axial deep venous insufficiency and twisted GSV. **Baseline characteristics:** (n represents number of legs). For baseline values of outcomes, variance given is range. Authors stated no group differences. But note the numerical difference in C4 disease.	EVL done under duplex guidance with a 980mm diode laser, with pulse mode, 1.5 sec impulse, 1.5 sec pause and 12W. GSV accessed percutaneously. Catheter advanced until 1-2 cm below saphenofemoral junction. **Common procedures:** Tumescent anaesthesia administered with a syringe with US guidance to the GSV. Post surgery, compressive bandaging applied, and then replaced with a class 1 compressive stocking left in situ for 2 weeks	High ligation and perforate invagination stripping performed through a groin incision of 4-6 cm, with flush division of the GSV and division of all tributaries behind the second level of the division. If the vein broke then attempts were made to remove it from a more distal position below the knee. **Common procedures:** See intervention column.	12 d, 1,3 and 6 months.	Physician outcomes - VVSS QoL – disease specific AVVSS QoL – general SF-36 Adverse events Treatment failure	Public health insurance research foundation of Denmark.

Reference	Study type	No. of patients			Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	the same treatment given to both legs (risk of artificial reduction in variance). No blinding achieved.							(not entirely clear this was used for EVL patients, however). Both groups also had multiple phlebectomies as needed. Diclofenac given as pain relief.				
			EVLA	Surgery		Surgery	EVLA					
		12 d	2	0	prev high lig	8/59	8/62					
		1 mo	4	2	M:F	16:43	21:41					
		3 mo	6	5	CEAP 2	51/59	50/62					
		6 mo	15	18	CEAP4	3/59	9/62					
					GSV diam (mm)	7.6 (2.1)	7.9 (2.7)					
					reflux time (s)	2.5 (1.0)	2.6 (1.1)					
					AVVSS	16.1 (4.4-34.3)	18.6 (3.6-40.2)					
					VCSS	2.4 (2-12)	2.8 (1-8)					
					SF36 – physical function	89.3 (25-100)	87 (25-100)					
					SF36 – role-physical	89.3 (25-100)	87 (25-100)					
					SF36 – bodily pain	77.1 (22-100)	76.6 (22-100)					

Reference	Study type	No. of patients			Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					SF36 – gen health	67.6 (28-80)	65.2 (32-80)					
					SF36 – vitality	73.1 (12.5-100)	69 (12.5-100)					

Results: For continuous variables, only mean and ranges given.

All outcomes measured at 3 months	**Stripping surgery**	**Endovenous laser ablation**
AVVSS 3 (score out of 100, with 100 worst symptoms)	8.2 (0-31.2)	6.9 (0-43.8)
VCSS	0.2 (0-2)	0.1 (0-2)
SF36 – physical function	92.2 (43.7-100)	93.9 (56.2-100)
SF36 – role-physical	92.2 (43.7-100)	93.9 (56.2-100)
SF36 – bodily pain	89.5 (31-100)	89.1 (32-100)
SF36 – gen health	66.7 (20-80)	67.7 (32-80)
SF36 – vitality	79 (37.5-100)	76.2 (18.7-100)
SF36 – social functioning	97.1 (12.5-100)	94.5 (37.5-100)
SF-36- role emotional	95.8 (58.3-100)	94.4 (33.3-100)
SF-36 – mental health	89.2 (60-100)	84.3 (25-100)
All outcomes measured at 6 months	**Stripping surgery**	**Endovenous laser ablation**
AVVSS (score out of 100, with 100 worst symptoms)	5.3 (0-33.1)	7.1 (0-38.7)
VCSS	0.2 (0-2)	0.4 (0-7)
SF36 – physical function	92.6 (50-100)	93.9 (43.7-100)
SF36 – role-physical	92.6 950-100)	93.9 (43.7-100)
SF36 – bodily pain	86.5 (20-100)	90.9 (51-100)
SF36 – general health	67 (33.6-80)	67.9 (40-80)
SF36 – vitality	82.9 (56.2-100)	77 (18.7-100)
SF36 – social functioning	98.8 (62.5-100)	98.2 (62.5-100)

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

SF-36- role emotional	95.7 (50-100)	95 (58.3-100)
SF-36 – mental health	90.2 (70-100)	86.2 (40-100)
Adverse events	**Stripping surgery**	**Endovenous laser ablation**
major complication – infection of groin (12days)	1/68	0/67
phlebitis (12days)	2/68	2/67
phlebitis (1month)	2/66	2/65
bruising (12days)	15/68	7/67
hematoma (12days)	5/68	3/67
hematoma (1month)	1/66	0/65
parasthsia (1 month)	0/66	1/65
paraesthesiae (6months)	1/50	0/54
NOT stripped /occluded 12 days	0/67	2/68
NOT stripped/occluded 1 month	0/65	2/66
NOT stripped/occluded 3 months	1/63	0/63
NOT stripped/occluded 6 months	3/53	1/50
time to resume normal activity (days)	7.7 (6.1)	6.9 (7)

Author's conclusions: The treatments were equally safe and efficient at eliminating GSV reflux.

Table 77: Rasmussen2010[220]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rasmussen LH, Bjoern L, Lawaetz M, Lawaetz B, Blemings A, Eklof B. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. Eur J Vasc Surg 2010: in press. Doi: 10.1016/j.ejvs.2009.11.040	RCT. Follow up to Rasmussen 2007	Follow up to Rasmussen 2007	Follow up to Rasmussen 2007	Follow up to Rasmussen 2007	Follow up to Rasmussen 2007	2 yrs	Recurrence Clinical severity score Quality of life	Public health Insurance Research Foundation of Denmark

Results:

AVVSS, VCSS and domains of the SF36 were reported to not differ at 2 years, but no data given (except in very low resolution figures)

	EVLA	**Surgery**	p
Recurrence (legs) at 2 years [note the denominators do not reflect the drop outs that occurred earlier in the study, so ITT? But no mention of ITT or imputation].	18/69	25/68	ns
Reflux into the AAGSV	6/69	3/69	
Reflux in the groin	2/69	3/69	
Reflux in thigh perforators	4/69	9/69	
Reflux in lower leg perforators	3/69	6/69	
Retreatment (mainly for cosmetic reasons)	9/69	6/69	

Table 78: Rasmussen2011[221]

See Table 63 for evidence table.

Table 79: Rass2011[222]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rass K, Frings N, Glowacki P, Hamsch C, Graber S, Vogt T, Tilgen W. Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein. Arch Dermatol 2011; ecopy published online	RCT. Randomisation method unclear. Allocation concealment likely through use of an independent remote centre for treatment allocation. Only one limb used per patient. If bilaterally affected the worst limb was used for the study. Each treatment given in a separate site,	400 randomised – 200 initially allocated to each group. 15 did not receive EVLT as they declined to participate. Of the 185 who received EVLT, 12 were lost to follow-up (11 refused or unavailable and 1 died). 39 did not	**Inclusion:** GSV insufficiency with SF incompetence and reflux to knee level; CVI and/or symptoms caused by GSV incompetence and/or severe clinical findings at risk of varicose vein bleeding, thrombophlebitis and DVT; age 18-65 years; performance status, according to the American Society of Anaesthesiologists of class 1-11. **Exclusion:** Previous groin surgery except inguinal herniotomy; ant or post accessory saphenous vein incompetence; small saphenous vein insufficiency requiring treatment; thrombophilia; PAD; Malignant disease diagnosed in past 5 years; pregnancy or lactation. **Baseline characteristics:** The baseline characteristics of those for whom outcome data is available are not shown. The baseline data below includes those lost to follow-up, and for whom no ITT was undertaken! | | EVLT | Surgery |	Endovenous Laser therapy done with a 810mm diode laser, using Seldinger's technique, and a 20W laser power. **Common procedures:** Tumescent anaesthesia administered. Both groups also had multiple phlebectomies as needed. Analgosedation using intravenous midazolam allowed at the surgeon's discretion given as pain relief.	Flush ligation of SFJ and invagination stripping of the GSV just below the knee. **Common procedures**: See intervention column.	Post op, 3 months, 1 year and 2 years.	Reflux Advers e events HVVSS (higher means worse) CIVIQ-2(higher means worse) Patient assessed symptoms	None reported

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	leading to risk that site effects, rather than treatment effects, could explain study results. Blinding not reported.	receive stripping as they declined to participate. Of the 161 who received stripping, 18 were lost to follow-up (18 refused or were unavailable). No ITT done – 173 evaluated in EVLT group and 143 evaluated in the stripping group. High risk of attrition bias due to differential loss to follow-up	Age	47.9(10.9)	48(10.7)					
			F	67%	70%					
			BMI	26.2(4.1)	26.3(4.9)					
			CEAP 2	53/185	47/161					
			CEAP3	95/185	76/161					
			CEAP4	36/185	35/161					
			CEAP5	1/185	2/161					
			CEAP6	0/185	1/161					
			HVVSS	16.1 (4.4-34.3)	18.6 (3.6-40.2)					
			GSV diameter at SFJ (mm)	8.7(2.8)	8.7(2.2)					
			CIVIQ-2	28.6(19)	29.4(16)					

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		rates and no ITT.								

Results: For continuous variables, only mean and ranges given.

	EVL	Surgery
Reflux at 2 years	31/173	2/143
Adverse events		
DVT	1/185	1/161
Phlebitis	20/185	4/161
Pain at 1 week	118/185	91/161
Pain (VAS) mean (sd) [higher worse]	1.6(0.8)	1.3(0.6)
Neural damage/injury 3 months		
Hyper-pigmentation 3 months	17/185	22/161
	57/185	19/161
HVSS 3 months	3.9(3)	3.8(3)
HVSS1 year	2(2)	2.1(3)
HVSS2 years	2.1(3)	1.9(3)
CIVIQ-2 [note only done on last 100 patients enrolled] – 3 months	12.8(14) [43]	18(16) [37]
CIVIQ-2 [note only done on last 100 patients enrolled] – 1 yr	10.5(14)[40]	11.1(14)[32]
CIVIQ-2 [note only done on last 100 patients enrolled] – 2 yrs	10.8(13)[41]	9.5(11)[33]
Pt reported pain from varicose veins (taken from CIVIQ) at 3 months	3(3)	4.6(4)

Author's conclusions: Both EVLT and HLS are comparably safe and effective procedures to treat GSV incompetence.

Table 80: Rautio2002[224]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H, Karjalianan P, Haukipuro K, Juvonen T. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomised controlled trial with comparison of the costs. JVasc Surg 2002; 35: 958-965.	RCT. Randomisation method unclear, but allocation concealment likely through sealed envelopes. No evidence of blinding. All treatments performed by the same single surgeon.	36 enrolled. 3 withdrew because of an unsuitable schedule and so 33 were randomised. After randomisation, 4 withdrew from the stripping group due to disappointment in being assigned to that group. A further patient withdrew from the EVRF group because of pregnancy. Hence drop out was surgery:4, EVRF 1. Ultimately 28 participated, 15 in the EVRF group and 13 in	Patients scheduled for surgical treatment of primary varicose veins. **Inclusion:** A valsalver manoeuvre-induced reversal of blood flow lasting > 2 seconds was considered the threshold for inclusion. Patients suitable for day case surgery with symptomatic, previously untreated and complicated GSV tributary varicosis and isolated unilateral SFJ and GSV trunk insufficiency were eligible for the study. **Exclusion:** Coagulopathy, multiple, tortuous and large diameter (>12 mm) GSV trunks were excluded. Veins with a curve >90 degrees. **Baseline characteristics:** Only age was deemed different between groups at baseline. Hence the small numbers in each group did not lead to chance differences of note at baseline. mean (sd) unless stated. EVRF | Surgery age: 33 (6.7) | 38 (6.8) F:M: 14:1 | 12:1	Stripping surgery. Groin dissected to expose the SFJ. Side branches of the GSV at the SFJ were divided and ligated. After local phlebectomy, the GSV was stripped from just below the knee to the groin with the venostrip with a 9mm olive. **Common procedures**: General anaesthetic given. Local phlebectomy and microsclerotherapy performed as necessary. Knee and groin anti-embolism stockings used for first 7 days.	Radiofrequency endovenous obliteration carried out with the VNUS Closure system (see Lurie studies). The catheter with sheathed electrode was inserted percutaneously with US scan guidance into the GSV at the ankle level, and then passed up to the SFJ. The entire length of the GSV was exsanguinated with compression and elevation, and the probe was then slowly withdrawn (3	7, 14, 28 and approx 49-56 days. Mean 50 days.	Physician reported outcomes (VSDS, VCSS, VDS). QoL (RAND 36) Post-operative pain Adverse events Treatment failure	not stated

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		the surgery group. A further patient “retired” [declined any treatment?] but was not withdrawn from the study. It is not reported from which group this patient was.	BMI	23.3(5.3)	24.0 (1.7)		cm/min). To avoid damage to the saphenous nerve, treatment was kept above the medial tibial condyle.			
			max GSV diam. (mm)	6.4 (1.7)	6.1 (1.3)					
			Office/light work	14/15	12/13					
			heavy work	1/15	0/13					
			retired	0/15	1/13					
			VCSS (median and range)	5 (4-9)	4 (4-6)					
			VSDS	1 (1-1)	1 (1-1)					
			VDS	1 (1-2)	1 (1-1)					
			operation time (mins)	75 (16.6)	57 (11)					
			Rand – 8 dimensions	All were similar across groups						

Results:

	EVRF	**Surgery**	p
VSDS (post operative). Median (range)	0 (0-0)	0 (0-1)	1
Decrease in VCSS [mean(sd)]. **Unclear time point.**	5.1 (1.5)	4.4 (1.1)	0.19
VDS (post operative). Median (range)	0 (0-1)	0 (0-1)	**1**

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse events (intraoperative)								
groin hematoma	0/15	1/13						
thermal skin injuries	3/15	0/13						
Adverse events (post-operative)								
saphenous nerve paraesthesiae	2/15	3/13						
clinical thrombophlebitis	3/15	0/13						
local heamatoma	1/15	4/13						
thermal skin injury	1/15	0/13						
total	7/15	7/13						
Post-op Pain at rest (VAS) averaged over first 14 days [mean(sd)]	0.7 (0.5)	**1.7 (1.3)**	0.017					
Post-op Pain on standing (VAS) averaged over first 14 days [mean(sd)]	1.3 (0.7)	2.6 (1.9)	0.026					
Post-op Pain when walking (VAS) averaged over first 14 days [mean(sd)]	1.8 (0.8)	3.0 (1.8)	0.036					
RAND Physical functioning 1 week [median(IQR)] for all	30 (21-48)	50 (35-65)	0.07					
RAND Physical functioning 4weeks	0 (-5-4)	5 (0-10)	0.11					
RAND role functioning physical 1 week	75 (38-100)	75 (25-100)	0.8					
RAND role functioning physical 4weeks	0 (0-0)	0 (-25 – 0)	0.9					
RAND bodily pain 1 week	23 (5-25)	38 (20-45)	0.05					
RAND bodily pain 4weeks	-23 (-28 -0)	-10 (-33-0)	0.6					
RAND general health perception 1 week	0 (0-8)	0 (-5 – 10)	0.7					
RAND general health perception 4weeks	-5 (-8 – 0)	-5 (-5-10)	0.7					
RAND energy 1 week	10 (-3 – 20)	0 (-10 – 15)	0.5					

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

RAND energy 4weeks	-10 (-10-0)	-10 (-25-10)	0.13
RAND social functioning 1 week	23 (0-31)	25 (13-50)	0.4
RAND social functioning 4weeks	0 (-13-0)	0 (0-0)	0.3
RAND role functioning emotional 1 week	0 (0-0)	0 (0-0)	0.9
RAND role functioning emotional 4weeks	0 (0-0)	0 (0-0)	0.5
RAND emotional well being 1 week	-4 (-6 – 4)	-4 (-8 -4)	0.7
RAND emotional well being 4weeks	-4 (-8 – 4)	-8 (-8-0)	0.4
Reflux	**0/15**	**1/13 (reflux in an accessory branch of the GSV**	
analgesic use (number of 600mg ibuprofen tabs/day	**0.4 (0.49)**	**1.3 (1.09)**	

Table 81: Stotter2006[256]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th colspan="3">Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="6">Stotter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping, and cryostripping in the treatment of great saphenous vein insufficiency. 2006; 21: 60-64.</td><td rowspan="6">RCT. Randomisation carried out by a statistical department, but no other details given, and no reports of allocation concealment.</td><td rowspan="6">60 patients (60 limbs).20 allocated to cryostripping (NA). 40 (20+20) allocated to the two groups of relevance. 1 lost from each group at 1 year follow-up.</td><td colspan="3">Inclusion: Primary varicose veins; >0.5sec reflux on duplex.
Exclusion: requiring avulsion phlebectomies in the thigh.
Baseline Characteristics: (all reported as not different):</td><td rowspan="6">Ligation and invagination stripping to just below the knee. to just below the knee.
Common procedures: General Anaesthetic</td><td rowspan="6">EVRF with VNUS closure system. Aim was to increase temp. To 85 deg C and the probe was retracted at 3cm/min.</td><td rowspan="6">24hrs, 1 week, 6 weeks, 1 year.</td><td rowspan="6">Treatment failure
Patient satisfaction
Physician global assessments</td><td rowspan="6">None</td></tr>
<tr><td></td><td>Surgery (n=)</td><td>EVLA (n=)</td></tr>
<tr><td>M:F</td><td>5:15</td><td>6:14</td></tr>
<tr><td>age</td><td>54 men; 51 women</td><td>41 men; 44 women</td></tr>
<tr><td>duration of pathology</td><td>7.1 yrs</td><td>9.6 years</td></tr>
<tr><td>GSV diam. Distal to saphenofemoral ostium</td><td>7.1 (5-14)</td><td>6.8(4.5-12)</td></tr>
</table>

Results: No variances given for continuous variables.

	Surgery	**EVLA**	
Physician global impression score (6 weeks?)[lower better]	0.86	0.62	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Treatment failure (immediate in terms of open segments)	0/20	1/20	
Hematoma surface area at 1 week (cm2)	109	55	
Numbers with heamatoma 24 hours	19/20	14/20	
Numbers with heamatoma 1 week	18/20	11/20	
Cumulative up to 6 weeks impairment score	7.9	2.8	
Cumulative up to 6 weeks pain score	7.5	4.6	
Adverse events up to 6 weeks			
DVT	0/20	0/20	
PE	0/20	0/20	
Saphenous nerve injury	0/20	0/20	
Treatment failure (Recanalisation or neovascularisation)		2/19	
Patient satisfaction with appearance of leg 1 year – very satisfied Patient satisfaction with appearance of leg 1 year –satisfied Patient satisfaction with appearance of leg 1 year – not satisfied	7/19 11/19 1/19	17/19 2/19 0/19	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Patient satisfaction with treatment 1 year – very satisfied	7/19	17/19	
Patient satisfaction with treatment 1 year – satisfied	12/19	1/19	
Patient satisfaction with treatment 1 year – not satisfied	0/19	1/19	

Table 82: Subramonia2010B [258]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th colspan="3">Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="5">Subramonia S, Lees T. Randomised clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. British Journal of Surgery 2010; 97: 328-336.
NB notes that its companion paper, the HE paper, is excluded and should go in exclusion list: Subramonia S, Lees T. Radiofrequenc</td><td rowspan="5">RCT. Randomisation using a web based randomisation method stratified for age and sex. No evidence of allocation concealment. No blinding.</td><td rowspan="5">93. 48 randomised to EVRF and 45 to surgery. No treatment: EVRF: 1; surgery 4 (not related to trial or treatment allocation). No further loss to follow-up. No ITT (i.e. those withdrawing from treatment not assessed, and no imputations made).</td><td colspan="3">Inclusion: Patients with symptomatic varicose veins (CEAP 2-6); primary or recurrent GSV reflux on duplex; patient fit for GA; ambulatory.
Exclusion: small saphenous or deep saphenous incompetence; twisted GSV above knee; GSV diam. <3 or >12mm; GSV thrombus; pacemakers or internal defibrillator; PAD [ABPI <0.9]; pregnancy.
Baseline characteristics: No differences reported.</td><td rowspan="5">Tributaries of the GSV ligated. GSV ligated (high ligation). PIN stripper used.
Common procedures: Multiple phlebectomies. Both groups had general anethetic. Above knee graduated compression stockings worn for 2 weeks. Activity advice given.</td><td rowspan="5">EVRF: GSV accessed percutaneously, and VNUS Closure catheter introducing, with tip just below superficial epigastric vein. With a target temperature of 85C the probe was withdrawn at a rate of 1.5-2 cm/min for the first 3cm and then 1-3cm per min for the rest of the GSV.</td><td rowspan="5">1 week, 5 weeks.</td><td rowspan="5">CEAP
Micheales classification
TCSS
VDS
AVVQ
VEINES-QoL/Sym</td><td rowspan="5">None</td></tr>
<tr><td></td><td>EVLA (n=47)</td><td>Surgery (n=41)</td></tr>
<tr><td>Age</td><td>47 (38-58)</td><td>45 (37-53)</td></tr>
<tr><td>M:F</td><td>13:34</td><td>14:27</td></tr>
<tr><td>CEAP2</td><td>37/47</td><td>33/41</td></tr>
</table>

Reference	Study type	No. of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
y ablation vs. conventional surgery for varicose veins – a comparison of treatment costs in a randomised trial. European journal of vascular and endovascular Surgery 2010; 39: 104-111.			CEAP3	9/47	7/41					
			CEAP 4-6	1/47	1/41					
			TCSS 0	25/47	27/41					
			TCSS 1	12/47	7/41					
			TCSS 2	4/47	1/41					
			TCSS 3	1/47	1/41					
			TCSS ≥4							
			VDS 0	2/47	2/41					
			VDS 1	44/47	35/41					
			VDS 2	1/47	4/41					
			ASA 1	36/47	34/41					
			ASA II	11/47	7/41					
			Recurrent	3/47	2/41					

Results:

	EVLA	**Surgery**	P
Immediate treatment failure (? As immediately rectified in the case of EVRF, not clear if we should refer to this as treatment failure)	2/47 (occlusion failure, detected on intra-op duplex, corrected after	7/41 (complete stripping not possible	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				immediate retreatment)	for these)			
1 week treatment failure (defined by duplex imagining of reflux in GSV)				0/47	5/41			
Adverse events								
cutaneous sensory abnormalities 1 week				9/47	20/41		**0.003**	
cutaneous sensory abnormalities 5 weeks				7/47	19/41		**0.003**	
parasthesia 1 week				5/47	11/41		**0.049**	
parasthesia 5 weeks				6/47	5/41		**0.936**	
groin wound problems 1 week				0/47	7/41			
non tender palpable GSV with overlying pigmentation 1 week				5/47	0/41			
pain level (VAS) during first week post op (med[IQR])				1.7 (0.5-4.3)	4 (2.35-6.05)		**95% CI= -2.75, -0.79**	
numbers with pain requiring anaesthesia post op				30/47	40/41			
satisfaction (VAS)(med[IQR])				10 (8.4-10)	8.5 (7.5-10)		**95% CI= 0.15, 1.44**	
Numbers completely satisfied (VAS score of 10)				27/47	11/41		**0.004**	
numbers unwilling to recommend the procedure to others				1/47	9/41		**0.005**	
TCCS and VDS				Incomplete outcome reporting; "more than three quarters in each group had an improved TCSS and VDS after surgery. Two patients, one in each group, had worsening of VDS by one point after treatment"				
improvement in AVVQ QoL score (mean; variance for each group not given, but CIs for the main difference given) 5 weeks [negative score				-9.12	-8.24		**-3.64, 1.89; p=0.532**	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

better]			
V-Q/Sym Q analysis improvement in symptom score (mean; variance for each group not given, but CIs for the main difference given) 5 weeks	12.62	9.94	**-1.65, 7.01; p=0.220**
V-Q/Sym Q analysis improvement in QoL score (mean; variance for each group not given, but CIs for the main difference given) 5 weeks	12.80	7.83	**0.80, 9.14; p=0.02**
improvement in AVVQ QoL score (mean; variance for each group not given, but CIs for the main difference given) 5 weeks	-9.12 (6.405) imputed by using the equation SE= (upper – lower CI)/3.92, and then converting SE OF THE MEAD DIFF to within gp sd for each. Actually /4.042 as used t dist for small sample of 40.	-8.24 (6.405)	

G.5.3 Foam sclerotherapy vs. endothermal ablation

Table 83: Rasmussen2011[221]

See Table 63 for evidence table

Table 84: Lattimer2012 [143]

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Lattimer CR et al. Cost and effectiveness of laser with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency. Early results of a randomised controlled trial. Eur J Vasc and Endovasc Surg 2012; 43: 594-600</td>
<td>Randomised controlled trial. Numbered sealed envelopes used so probable allocation concealment. Blinding not carried out. Strictly 1 leg per participant- if bilateral the worse leg was studied.</td>
<td>110 randomised – 56 EVLA and 54 FS. 6 did not receive EVLA or switched groups and 4 did not receive FS or switched groups. Per protocol analysis used as only those completing treatment (50 and 50) analysed at 3 week follow-up. Then 4 and 5 (respectively) lost to follow-up at 3 month follow-up. Overall, the loss was comparable across groups so minimal risk of selection bias.</td>
<td>Inclusion: Primary symptomatic VV; SFJ reflux on duplex; suitable for both techniques.
Exclusion: SPJ incompetence, GSV >12mm; prev surgery or FS of study leg; history of DVT; arterial occlusive disease (ABPI<0.8); active malignancy; pregnancy; known relevant allergies.
Baseline Characteristics
<table>
<tr><th></th><th>EVLA</th><th>Foam sclero</th></tr>
<tr><td>Age</td><td>47.4 (21-74)</td><td>48.5 (22-78)</td></tr>
<tr><td>Female</td><td>62%</td><td>54%</td></tr>
<tr><td>Bilat disease</td><td>56%</td><td>64%</td></tr>
<tr><td>CEAP</td><td></td><td></td></tr>
<tr><td>2</td><td>44%</td><td>20%</td></tr>
<tr><td>3</td><td>14%</td><td>16%</td></tr>
</table>
</td>
<td>Outpatient FS – max 12ml foam. 1% STDS used. Injected into saphenous trunk at knee level. Tributaries treated as required on a subsequent occasion using a 21 gauge needle.</td>
<td>EVLA to GSV in day surgery theatre, using ELVes painless diode laser; 1470 nm; tumescent anaesthesia used. Access point near knee. Incompetent saphenous tributaries treated concurrently.</td>
<td>3 months</td>
<td>AVVQ
VCSS
Reflux
Post procedure pain
Return to normal activities</td>
<td>STD pharmaceuticals</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			4	30%	48%					
			5/6	12%	16%					
			VCSS	6 (2-20)	7 (3-17)					
			AVVQ	20 (1-53)	25 (4-50)					
			VFI	4.7 (0.9-17.8)	5.9(1.1-15.5)					
			GSV diam	7 (4-12)	8 (5-12)					
			BK GSV reflux	58%	74%					

Results

	EVLA	**Foam Sclerotherapy**	p
Median (IQR) pain for 7 days after treatment (VAS score with 100 worst pain)	33(18-54)	14(6-34)	P=0.005 Man Whitney U test
Median (IQR) time to return to normal activities	7.5(2-15)	3(1-10)	P=0.011 Man Whitney U test
Median days requiring analgesia tablets	2(0-21)	0(0-14)	
Reflux (Above knee) 3 weeks	1/50	8/50	
Reflux (Above knee) 3 months	9/46	9/45	
Reflux (Below knee) 3 weeks	7/50	24/50	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reflux (Below knee) 3 months	21/46	19/45	
Need for further treatment	3/50	28/50 (but this may be because concurrent treatment unavailable for FS group, in contrast to EVLA group)	
Median (IQR) AVVQ at 3 months	5.8(2.5-12.2)	12.4(6-21.9)	
Median (IQR) VCSS at 3 months	1(0-3)	2(1-4)	
Median (IQR) VFI at 3 months	1.5(1.1-2.4)	1.9(1.3-2.7)	
Change from baseline in AVVQ by 3 months	12	9	0.062
Change from baseline in VCSS by 3 weeks	3	3	0.721
Change from baseline in VCSS by 3 months	5	4	0.817
Change from baseline in VCSS VFI by 3 months	2.6	3.1	0.791
Adverse event: DVT	1/50	0/50	
Adverse event: thrombosis	2/50	8/50	

Table 85: Gonzalez-Zeh2008[107]

<table>
<tr><th>Reference</th><th>Study type</th><th>No of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Gonzales-Zeh R, Armisen R, Barahona S. Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one year follow-up results. Journal of vascular surgery 2008; 48: 940-6.</td>
<td>Prospective cohort study (effectively a non-randomised trial). Patients were told each treatment option was equivalent and were allowed to choose their own group [NB this probably carries less of a bias risk than physician allocation, as less risk, albeit in the internet age, of allocation based on prognostic characteristics]. Only one limb per patient was included and treated in this study. A single surgeon with experience of 800 EVLA procedures and 2000 foam sclerotherapy</td>
<td>98. No patients dropped out and all followed up.</td>
<td>Inclusion: Primary incompetence of the GSV and SFJ insufficiency with a reflux time of 0.5 seconds measured over a distance of at least 20cm in the upper leg.

Exclusion: pregnancy; active thrombophlebitis, clotting disturbances; thrombophilia or coagulation disorders; history of DVT; history of malignancies.

Baseline characteristics: Despite the lack of randomisation the groups were well matched.
<table>
<tr><th></th><th>EVLA</th><th>Sclero</th></tr>
<tr><td>n</td><td>45</td><td>53</td></tr>
<tr><td>M:F</td><td>7:38</td><td>11:42</td></tr>
<tr><td>Age</td><td>51.1(11.9)</td><td>53.7(12)</td></tr>
<tr><td>CEAP</td><td>15/4</td><td>16/53</td></tr>
</table>
</td>
<td>US guided foam sclerotherapy. Policodanol was used with a sclerosant to air ratio of 1:4. Single injection using a venflon of 3% foam applied with the patient in supine. Injection at the point of most distal reflux in GSV. Volume of injection decided by surgeon. Immediate 2 minute compression applied afterward.

Common procedures: Full length class II compression stocking applied 10 minutes post procedure with the patient lying down. The stockings were to be continued for 7 days and nights continuously and for 7 additional days where usage in the day only was required. Patients advised to walk for 30 minutes immediately</td>
<td>Endovenous laser ablation. GSV at the point of most distal reflux was punctured with a 21 gauge needle under US guidance, and a guide wire passed up the GSV, followed by a 5 Fr introducer sheath to a point 1cm below the SFJ. 600 micron laser filament passed through the sheath to a point 1 cm below the SFJ. Then it was withdrawn at 1-2 mm/sec in continuous mode, with energy delivered by a 980 nm diode laser at a power of 15 W.

Common procedures: See intervention</td>
<td>1 week, 1 month, 6 months and 1 year.</td>
<td>Reflux

VSCC</td>
<td>Not stated</td>
</tr>
</table>

Reference	Study type	No of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	procedures did both interventions. Patients were not allowed to mix, to avoid contamination of patient expectations. **Clinical and ultrasound follow-ups done by a blinded assessor.**		2 3 4 5 6	5 16/45 9/45 3/45 2/45	16/53 10/53 6/53 5/53	post procedure and to walk daily for 30 minutes. Simple non-prescription analgesia allowed for pain.	column.			
			superficial	45/45	45/53					
			VCSS (median[IQR])	3 (3-5)	3 (3-5)					

Results

	EVLA	**Foam sclerotherapy**	p
Reflux at 7 days (not all reflux, includes open and flux)	0/53	4/45	not given
Reflux at 6 months (not strictly reflux, but referred to as partial recanalisation)	1/53	2/45	not given
Reflux at 1 year (true reflux)	1/45	8/45	**0.0360**
Non occlusion at one year	3/45	12/45	0.04650
VCSS at 1 year (only includes those with no recanalisation at one year) [median (IQR)]	3(3-2)	2(3-2)	No p for between group effects

Adverse events

pain (VAS 1-10, 10 worst)	4.9 (1.5); n=45	4.0 (1.5); n=53	0.0082
phlebitis	10/45	22/53	0.0529
paraesthesia	2/45	1/53	0.5923
DVT	0/45	2/53	0.4982

G.5.4 Truncal and tributary treatment vs. truncal treatment alone

Table 86: Carradice 2009[46]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Carradice D, Mekako AI, Hatfield J, Chetter IC. Randomised clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. British Journal of Surgery 2009; 96: 369-375</td>
<td>RCT. “randomised to one of two groups using sealed envelopes”. Thus allocation concealment likely, but method of randomisation unclear.</td>
<td>50, 25 randomised to each group. Per-protocol analysis used. In the truncal +tributary group one was lost to follow-up by 6 weeks, and all received intervention. In the trunk only group, one was withdrawn after not receiving intervention, and none others lost to follow-up by 6 weeks. Thus 24 in each group analysed (4% loss in each – unlikely to cause bias) at 6 weeks. At 3 months, further losses to follow-up led to 23 in the truncal</td>
<td>Inclusion: Patients with primary, unilateral, symptomatic great saphenous varicose veins; SFJ incompetence and GSV reflux on duplex; perigenicular vein diameter > 4mm.
Exclusion: Saphenopopliteal, small saphenous or deep venous incompetence on duplex.
Baseline Characteristics: Comparable for all baseline variables.
<table>
<tr><th></th><th>truncal + tributary</th><th>truncal alone</th></tr>
<tr><td>age</td><td>51.1(14.3)</td><td>52.5(15.6)</td></tr>
<tr><td>M:F</td><td>8:17</td><td>4:21</td></tr>
<tr><td>VCSS</td><td>4(2.25-5)</td><td>4(2-5)</td></tr>
<tr><td>SF-36 physical</td><td>85(70-99)</td><td>93(80-100)</td></tr>
<tr><td>SF-36 bodily pain</td><td>74(51-84)</td><td>79(55-100)</td></tr>
</table>
</td>
<td>Endovenous laser therapy - cannulation at the GSV. 600nm laser fibre introduced, delivering 14 W continuous 810 nm laser. Target energy delivery was 80-100 J/cm. Concomitant ambulatory phlebectomy of varicosities also carried out. Stab incisions of 1-2mm made over varicose tributaries, and veins avulsed.
This is not clear, but looks likely that</td>
<td>Endovenous laser therapy as for intervention group, but with no concomitant procedures. Sequential ambulatory phlebectomies allowed after 6 weeks if required.</td>
<td>6 weeks (after 6 weeks, sequential ambulatory phlebectomies allowed after this time in the comparison group). Further follow-ups were used at 3 months and 1 year.</td>
<td>AVVQ
SF36 & EQ-5D
VCSS
Return to normal activity and work
Post procedure pain
Obliteration
Need for further</td>
<td>None specified</td>
</tr>
</table>

Reference	Study type	No. patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		+ tributary group and 22 in the trunk only group, and at 1 year the analysed figures were 20 and 21 respectively.	AVVQ	13.29(11.09-15.50)	13.75(11.67-15.82)	BOTH groups had an elastic bandage applied to the leg for 1 week, and replaced by a class II (20-30 mmHg) full length graduated support stocking for a further 5 weeks.			procedures	
			EQ-5D	0.796(0.769-1)	0.796(0.778-1)					

Results:

	Trucal + tributary	Truncal only	p
AVVQ 6 weeks (lower better) [median(IQR)]	7.9 (4.1 – 10.7)[24]	13.5 (10.9 – 18.1)[24]	<0.001
AVVQ 3 months	2.0 (0.4-7.7) [23]	9.6(2.2 – 13.8) [22]	0.015
SF-36 EQ-5D	no results given in text (only in low resolution graph)		
Reflux at 1 week	0/24	0/24	
SFJ Reflux at 1 year	1/20	2/21	
GSV reflux at 1 year	2/20	1/21	
VCCS at 1-6 weeks (lower better)	no data	no date	
VCSS at 3 months	0(0-1) [23]	2(0-2) [22]	<0.001
VCSS at 1 year	0(0-1) [20]	1(0-1) [21]	0.433
Adverse events			
phlebitis	0/24	1/24	
pigmentation	2/24	0/24	

Reference	Study type	No. patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
thigh “neuralgia”			1/24	0/24				
post op pain			no data but recorded no difference between groups at days 1,3 and 7					
return to work (days)			10 (4-21)	3(1-14)			0.054	
return to normal activity (days)			8(1-14)	2(1-5)			0.166	
need for subsequent ambulatory phlebectomy at 6 weeks			1/25	16/24				
Patient satisfaction (would recommend to a friend or would have it again)			20/20	19/21				

G.6 Chapter 10 – compression after interventional treatment

Table 87: Hamel-Desnos 2010[111]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hamel-Desnos CM, Guias BJ, Desnos PR, Mesgard A. Foam sclerotherapy of the saphenous veins: randomised controlled trial with or without compression. Eur J Vasc Endovasc Surg 2010; 39: 500-507	RCT. Method of randomisation unclear. It is stated that randomisation was done 5-10 minutes after sclerotherapy using a randomisation list provided by the statistician. It is therefore likely that there was no allocation concealment. There were two study centres and two regions of treatment (great or small saphenous vein) and randomisation was stratified for these. No	60 (31 in combination, 29 in sclerotherapy only). No drop-outs reported.	**Inclusion:** Patients_presenting for treatment of symptomatic varicose veins; aged >18; incompetence of the GSV or SSV; trunk diameter >8mm for GSV and 6mm for SSV; venous reflux lasting at least 1 sec; C2-6. **Exclusion:** Any factors limiting the ability to participate in an informed manner; isolated SFJ incompetence; post-surgical recurrence of varices without trunk recurrence; chronic liver or renal disease; pregnancy/lactation; malignancy; history of DVT; cardio-vascular/respiratory problems; Coagulopathy; alcohol intolerance; allergies; patent foramen ovale; previous migraine or CNS disturbance after sclerosing therapy; lycra allergy; inability to apply compression. Only difference was for age(p=0.018); overall mean	Foam sclerotherapy using one volume of aetoxisclerol and 4 volumes of sterile air. Up to 3 sessions were permitted. 5-10 minutes after the first sclerotherapy session, class 2 French standard 15-20 mmHg stockings (thigh length for GSV and knee length for SSV) were applied, to be worn during the day for 3 weeks following	Foam sclerotherapy using one volume of aetoxisclerol and 4 volumes of sterile air. Up to 3 sessions were permitted. No compression given.	1 month	reflux at 1 month after treatment. QoL Patient assessed symptoms Adverse events	Some funding (for stats) by compression stocking company, as well as free stockings.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td>mention of blinding.</td><td></td><td>CEAP class was 2.6 (range 2-6)
Baseline Characteristics:
<table>
<tr><th></th><th>Sclero + compression</th><th>sclero only</th></tr>
<tr><td>age</td><td>61(11)</td><td>53(14)</td></tr>
<tr><td>%men</td><td>13</td><td>3</td></tr>
<tr><td>GSV affected</td><td>19/31</td><td>17/29</td></tr>
</table></td><td>treatment.</td><td></td><td></td><td></td><td></td></tr>
</table>

Results:

	Sclerotherapy plus compression	**Sclerotherapy only**	**p**
Reflux at 28 days	0/31	0/29	
CIVIQ 2 QoL global score – change from baseline day 14 (-ve change = improvement)	-5.5 (10) [22]	-9 (9.9) [21]	
CIVIQ 2 QoL global score – change from baseline day 28 (-ve change = improvement)	-9.4 (10) [23]	-11 (14) [24]	
rate of improvement at day 28			reportedly no difference between groups
heavy legs	(20/30) 67%	(16/29) 55%	
pain	(21/30) 70%	(17/29) 59%	
oedema	(15/30) 50%	(15/29) 52%	
paraesthesia	(17/30) 57%	(13/29) 45%	
cramp	(11/30) 37%	(16/29) 55%	
NB: the denominator of 30 for the combination group and 29 for the sclera only group led to the best agreement with the percentages given in the paper (no denominators given in the paper).			
Patient satisfaction with sclerotherapy “very effective” day 14 “very effective” day 28	 15/30 22/30	 20/29 19/29	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Patient satisfaction with COMPRESSION “very effective” day 14		7/30	
Adverse events			
major neurological events <24 hrs	0/31	0/29	
visual disturbance (scotoma) resolving within 15 mins	0/31	1/29	
moderate pain day 28	1/30	3/29	
pigmentation	2/30	1/29	
thrombophlebitis	3/30	3/29	
compliance with compression number wearing every day mean number of days use (max 21days)	 12/30 11		

Table 88: Houtermans-Auckel 2009[118]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. patients</th><th colspan="3">Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="6">Houtermans-Auckel JP, van Rossum E, Teijink JAW, Dahlmans AAHR, Eussen EFB, Nicolai SPA, Welton RJTJ. To waer or not to wear compression stockings after varicose vein stripping: a randomised controlled trial. Eur J Endovasc Surg 2009; 38: 387-391.</td><td rowspan="6">RCT. Randomised using computer generated randomisation list. Closed envelopes used, with pre-randomisation allocation concealment. No blinding after randomisation.</td><td rowspan="6">104 randomised – 52 allocated to each group. 2 patients in the comparison group and 6 patients in the intervention group dropped out 3 days post-operatively (prior to starting the 4 weeks compression). These drop-outs were thus not due to lack of efficacy or adverse events of compression as an adjunct, and this unlikely to cause bias. All unavailable for follow-up. Available case analysis done, with 46 analysed in the intervention group and 50 in the comparison group.</td><td colspan="3">Inclusion: Primary varicose veins due to GSV reflux; complete incompetence of the GSV on duplex US; C2-C3;
Excluson: Patients unable to wear compression stockings; patient who had already used compression stockings; patients with ulcers.
Baseline Characteristics:
Described as comparable.</td><td rowspan="6">Crossectomy and short GSV inversion stripping, done as day surgery, 90% of which was under spinal anaesthetic. Standard elastic bandaging with a rolled gauze over the proximal part of the GSV applied for 3 days.
Then fitted with class 2 medical compression stockings (measured fit), at 23-32 mmHg for 4 weeks, day and night for the first 2 weeks and then day only for the final 2 weeks.</td><td rowspan="6">Crossectomy and short GSV inversion stripping, done as day surgery, 90% of which was under spinal anaesthetic. Standard elastic bandaging with a rolled gauze over the proximal part of the GSV applied for 3 days.
No further compression given.</td><td rowspan="6">4 weeks post-op</td><td rowspan="6">post –op pain (VAS)
Post operative adverse events
Return to full activity</td><td rowspan="6">None</td></tr>
<tr><td></td><td>Ix</td><td>Comparison</td></tr>
<tr><td>Men%</td><td>27</td><td>37</td></tr>
<tr><td>age</td><td>50</td><td>49</td></tr>
<tr><td>R leg %</td><td>69</td><td>73</td></tr>
<tr><td>Muller phlebectomy done as well</td><td>52</td><td>48</td></tr>
</table>

Reference	Study type	No. patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results:

	Surgery plus compression	**Surgery only**
Adverse events		
post op pain (VAS) at 3 days	2.5(2.8)[46]	1.8(2.2)[50]
post op pain (VAS) at 2 weeks	2.2(2.3)[46]	2.2(2.4)[50]
post op pain (VAS) at 4 weeks	0.8(1.5)[46]	0.5(0.8)[50]
Numbness 3 days	4/46	3/50
Numbness 3 days	0/46	2/50
Numbness 3 days	0/46	0/50
Bleeding 3 days	0/46	0/50
Infection 3 days	2/46	1/50
Seroma 3 days	2/46	1/50
Return to work (measured at 4 weeks)	15(8.4)[46]	11(7.5)[50]

G.7 Chapter 11 - Pregnancy

Table 89: Mota-Capitao 1995[175]

Reference	Study type	No. of patients	Patient characteristics	Risk factors studied	Outcome measures	Length of follow-up	Source of funding
Mota-Capitao L, Menezes JD, Gouveia-Oliveira A. Clinical predictors of the severity of chronic venous insufficiency of the lower limbs: a multivariable analysis. Phlebology 1995; 10: 155-159.	Cross-sectional for many variables, but effectively a case-study for the potentially prognostic variables of family history and past medical history.	474 patients presenting to 18 different GPs with CVI symptoms.	Not all patients had CVI. 4% were class 0 CVI (asymptomatic), 42% class 1 (mild), 33% class 2 (moderate) and 21class 3 (severe). 70% had a history of varices. 3% had a history of DVT. 90% had had symptoms for > 1 year. HHD used to "confirm" diagnosis.	Many "risk factors" in this study were measured cross-sectionally, but potentially prognostic variables are age, sex, pregnancy, parity, hormones, family history, medication and past medical history.	A linear relationship between the risk factors and the ordinal outcome variable (class of CVI) was taken as evidence of an association of the risk factor with progression of CVI. However, only retrospective risk factors could be said to have a causative effect.	NA	Not stated

Results:

After multivariable analysis of factors having a linear relationship with CVI class, the potentially prognostic variables that remained in the model were as follows:

Factor	co-efficient	p
age	0.036	<0.001
CVI in both parents	0.568	0.026
History of thrombophlebitis	0.775	0.019
History of post-thrombotic syndrome	1.627	0.028
History of lymphoedema	1.712	0.026

Table 90: Fischer 2006[98]

See Table 26 for evidence table.

Table 91: Zubilewicz 2009[290]

See Table 21 for evidence table.

Table 92: Thaler 2001[260]

<table>
<tr><th>Reference</th><th>Study type</th><th>No. of patients</th><th colspan="4">Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="5">Thaler et al. Compression stockings prophylaxis of emergent varicose veins in pregnancy: a prospective randomised controlled study. Swiss Med Weekly 2001; 131: 659-662.</td><td rowspan="5">Randomised controlled study. No blinding for patients or HCP but blinding of assessors. No mention of randomisation method nor of allocation concealment. Stratified randomisation for venous status at entry (slight varicose changes present/abs</td><td rowspan="5">45 randomised. 3 drop outs from treatment in group 1 of the intervention group (see Intervention column) due to miscarriage, relocation abroad and failure to re-attend. No drop outs in the other groups. There were 9 losses of final follow-up data (controls: 3, group 1: 2; group 2: 4) but all were included in the analysis using earlier follow-up measures. Attrition bias</td><td colspan="4">Inclusion: Pregnant women with uncomplicated pregnancies <12 weeks gestation; absence of GSV reflux at SFJ.

Exclusion (post entry): intolerance of compression; miscarriage

Baseline characteristics:</td><td rowspan="5">Two treatment groups: group 1 wore class I compression tights on the left leg and class II on the right leg; group 2 wore class II compression tights on the left leg and class I on the right leg; This mirror division was to exclude a laterality bias in varicose vein emergence. However for</td><td rowspan="5">No stocking control group</td><td rowspan="5">Up to 6-8 weeks post-partum</td><td rowspan="5">Emergence of any varicose veins (including reticular veins)
Duplex evidence of GSV reflux (>2 secs).</td><td rowspan="5">Ganzioni, a stocking manufacturer, provided stockings and “logistic support”.</td></tr>
<tr><td></td><td>Controls</td><td>Gp 1</td><td>Gp 2</td></tr>
<tr><td>Maternal age</td><td>28.8(5)</td><td>29(5)</td><td>33(4)</td></tr>
<tr><td>parity</td><td>2(1.4)</td><td>1.7(0.9)</td><td>2.2(0.8)</td></tr>
<tr><td>Numbers with varicose veins at entry</td><td>9/15</td><td>7/12</td><td>8/15</td></tr>
</table>

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	ent).	minimal as there was only a 10% differential in drop out between combined group 1,2 and the controls.		the purposes of the review the results for group 1 and 2 have been merged.				

Results:

	controls	Group 1	Group 2	p
Patients with emergent varicose veins at 1 week post-partum	7/14	5/12	8/14	0.94
		13/26		
Patients with emergent third trimester GSV reflux at the SFJ during 3rd trimester	4/15	1/27		0.047
Leg symptoms at one week postpartum – better than baseline	0/14	3/12	4/14	0.03
		7/26		

Appendix H: Evidence tables economic studies

H.1 Chapter 7 – assessment for treatment

Table 93: Blomgren 2006A

L. Blomgren, N. Zethraeus, G. Johansson, B. Jonsson, and D. Bergqvist. Cost consequences of preoperative duplex examination before varicose vein surgery: a randomized clinical trial. *Phlebology* 21 (2): 90-95, 2006.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CC **Study design:** RCT – Within trial analysis **Approach to analysis:** Comparison of costs arising in the first 2 years of varicose vein treatment **Perspective:** Care-giver in Sweden (direct costs only) **Time horizon:** 2 years **Discounting:** Costs = 3%;	**Population:** Patients aged 20-75 admitted to hospital with varicose veins. Excluding those with pure cosmetic complaints, previous venous surgery or sclerotherapy, history of suspected or manifest deep venous thrombosis, active or healed leg ulcer, peripheral arterial disease, previous significant trauma to the leg, general illness and drug or alcohol abuse. Mean age: Duplex = 48 years, No duplex = 45 years. Gender: Duplex = 37% male, No duplex = 33% male **Intervention 1:** Duplex for pre-operative examination on top of participating surgeons' standard procedure for	**Mean cost per patient:** Intervention 1: SEK 13,051 (£900) Intervention 2: SEK 11,193 (£772) Incremental (2-1): SEK 1,858 (£128) **Currency & cost year:** 2004 Swedish krona (presented here as 2004 UK pounds[a]) **Cost components incorporated:** Costs for staff, physicians, colour flow duplex imagers and overhead costs, operating room costs (including salaries for anaesthetic and theatre staff, drugs, materials for cleaning and draping, gowns and	**Quality of Life:** No significant difference (no further data reported).[25]	**ICER:** NR **Analysis of uncertainty:** Uncertainty was not explored.

	clinical examination (varied by surgeon, sometimes included hand-held Doppler testing).[24] **Intervention 2:** Participating surgeons' standard procedure for clinical examination (varied by surgeon, sometimes included hand-held Doppler testing) only.	gloves), extra operative costs (ie for preoperative mapping), and admission costs if the patient was required to stay overnight.		
Data sources				
Cost sources: All costs were taken from the hospital accounting system (Capio St Göran's Hospital, Stockholm, Sweden).				
Comments				
Source of funding: NR. **Limitations:** The time horizon was restricted to two years and thus may not fully capture cost differences between the different assessment strategies; costs of re-treatment post 2 years which are likely to favour use of duplex will not have been captured. Uncertainty is not formally explored, but the authors note that with a longer follow-up the use of duplex could be cost-saving. QALYs are not considered, therefore no ICER can be presented. Finally, unit costs and resource use estimates are obtained from the trial only, rather than via a systematic procedure.				
Overall applicability[b]: Partially applicable Overall quality[c]: Potentially serious limitations				

Abbreviations: CC = cost comparison; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years; SEK = Swedish Krona

(a) Converted using 2004 purchasing power parities[195]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations /Potentially serious limitations / Very serious limitations

H.2 Chapter 8 – conservative management

Table 94: GOHEL2010[106] See Table 97: GOHEL2010

Table 95: MICHAELS2006[170]

J. A. Michaels, W. B. Campbell, J. E. Brazier, J. B. Macintyre, S. J. Palfreyman, J. Ratcliffe, and K. Rigby. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol.Assess.* 10 (13):1-196, 2006.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision-analytic Markov models were built for three different patient groups. **Approach to analysis:** Cost effectiveness modelling was over a period of 10 years (120 cycles). The analysis was not based solely on data from the 2-year randomized controlled trial because of small sample size. A separate within-trial economic analysis was also carried out; results are as in	**Population:** Patients with primary varicose veins. Subgroups: 'moderate' varicose veins with reflux; and 'severe' varicose veins. **Cohort settings:** Start age = 46 years Female = 90% **Intervention 1:** Conservative treatment **Intervention 2:** Standard surgery (saphenofemoral ligation, stripping and multiple phlebectomies) Liquid sclerotherapy was also included as a comparator; results are not presented here.	**Mean cost per patient:** *Moderate varicose veins* Intervention 1: £473 Intervention 2: £920 Incremental (2-1): £447 *Severe varicose veins* Intervention 1: £0 Intervention 2: £880 Incremental (2-1): £880 **Currency & cost year:** 2003 UK pounds **Cost components incorporated:** Initial costs of treatment (surgery, sclerotherapy), costs of retreatment, hospital admission/visits, visits to the GP, practice nurse and other healthcare professionals	**Primary outcome measure:** QALYs (mean per patient) *Moderate varicose veins (Group 2)*Intervention 1: 6.589 QALYs Intervention 2: 6.803 QALYs Incremental (2-1): 0.214 QALYs *Severe varicose veins (Group 3)*Intervention 1: 6.341 QALYs Intervention 2: 6.795 QALYs Incremental (2-1): 0.454 QALYs	***Moderate varicose veins (Group 2)*** **Intervention 2 versus Intervention 1:** ICER: £2,089 per QALY gained (d/a) ***Severe varicose veins (Group 3)*** **Intervention 2 versus Intervention 1** ICER: £1,938 per QALY gained (d/a)† **Analysis of uncertainty:** Univariate sensitivity analysis performed on: costs of surgery, costs of major complications after surgery, probability of residual veins after surgery, probability of minor complications after surgery and difference in the progression rate of reflux versus no reflux. Generally, the cost-effectiveness results are fairly robust to the univariate and multivariate sensitivity analyses. All ICERs fall below £20,000 per QALY.

<table>
<tr><th colspan="5">J. A. Michaels, W. B. Campbell, J. E. Brazier, J. B. Macintyre, S. J. Palfreyman, J. Ratcliffe, and K. Rigby. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). <i>Health Technol.Assess.</i> 10 (13):1-196, 2006.</th></tr>
<tr><td>Radcliffe et al (2006)[223]
Perspective:
UK NHS
Time horizon: 10 yrs
Treatment effect duration: 10 yrs
Discounting: Costs = 3.5%; Outcomes = 3.5%</td><td></td><td>(e.g., visits to the A&E and anticoagulation units).
Also included are costs of developing major or minor surgical complications, and costs of co-morbidity.</td><td></td><td></td></tr>
<tr><td colspan="5">Data sources</td></tr>
<tr><td colspan="5">Health outcomes: Some outcomes (for example, risk of complications following surgery or sclerotherapy, and rate of progression/recurrence of varicose veins) were taken from the randomized controlled trial contained in the report. Other outcomes (for example, probability of progression with reflux and progression without reflux) were informed by systematic reviews including Rigby et al. 2004[228].
Quality-of-life weights: Derived from SF-6D and EQ-5D scores. SF-6D scores were calculated from SF-36 data using an algorithm developed by Brazier et al. 2002[34].
Cost sources: Unit costs for all resources used by patients in the randomized controlled trial were obtained from the data sources in the UK including the NHS Reference costs, the Personal Social Services Research Unit and the British National Formulary (BNF). Data on resources use collected from the randomized controlled trial.</td></tr>
<tr><td colspan="5">Comments</td></tr>
<tr><td colspan="5">Source of funding: NHS R&D Health Technology Assessment (HTA) programme; Limitations: The retreatment options and rates of retreatment modelled are based on expert opinion, although no detail is given on the expert(s) or how this information was elicited. The clinical pathway is based on strict assumptions of who can receive which treatment, and may not fully reflect what happens in current practice. Utility data is based on an average of SF-36 and EQ-5D data; no reason is given.</td></tr>
<tr><td colspan="5">Overall applicability*: Directly applicable Overall quality**: Minor limitations</td></tr>
</table>

Abbreviations: CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported.

†The within trial analysis was conducted for this group – results are as presented in Ratcliffe et al 2006 (Table 96)

^ Surgery shows extended dominance over sclerotherapy in that a blend between conservative treatment and surgery offers better value for money than sclerotherapy;

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Table 96: RATCLIFFE2006[223]

J. Ratcliffe, J. E. Brazier, W. B. Campbell, S. Palfreyman, J. B. Macintyre, and J. A. Michaels. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. *Br.J.Surg.* 93 (2):182-186, 2006.

Study details	Population & interventions	Costs[†]	Health outcomes[†]	Cost effectiveness[†]
Economic analysis: CUA **Study design:** A randomized controlled trial conducted at two vascular units within the NHS. **Approach to analysis:** Economic analysis based on the 2-year data from the randomized controlled trial **Perspective:** UK NHS **Time horizon:** 2 years **Treatment effect duration:** 2 yrs **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Population:** Patients with uncomplicated varicose veins and evidence of saphenofemoral or saphenopopliteal reflux. Patients with recurrent varicose veins were excluded. **Cohort settings:** Start age = NR Male/ Female = NR **Intervention 1:** Conservative treatment (compression therapy plus lifestyle advice) N=124 **Intervention 2:** Stripping surgery N=122	**Mean per patient:** Intervention 1: £345 Intervention 2: £733 Incremental (2-1): £389 (95% CI: 282 to 506; p < 0.05) **Currency & cost year:** 2002-2003 UK pounds **Cost components incorporated:** Hospital inpatient admissions, surgical treatments, outpatient visits, other NHS visits (to the A&E, anticoagulation clinics, GP or practice nurse), retreatment costs, compression hosiery and treatment of complications.	**Primary outcome measure:** QALYs per patient (using SF-6D scores, n=94) Intervention 1: 1.420 QALYs Intervention 2: 1.503 QALYs Incremental (2-1): 0.083 QALYs (95% CI: 0.005 to 0.162; p < 0.05) **Other outcome measures (mean):** QALYs per patients (using EQ-5D values, n=91) Incremental (2-1): 0.133 QALYs	**Intervention 2 versus Intervention 1 (using SF-6D scores):** ICER: £4,682 per QALY gained (pa) 95% CI for ICER: £2,039 to £20,830 per QALY gained Probability cost-effective: With a threshold of £20,000 per QALY and QALY estimates based on SF-6D scores, the probability that surgery is cost-effective was 70%. At a £30,000 per QALY threshold, the probability increases to 76%. **Analysis of uncertainty:** Uncertainty around cost-effectiveness was assessed using bootstrap methods. The percentiles from the bootstrap replications were used to derive the cost-effectiveness acceptability curve. Sensitivity analysis showed that the economic results are fairly robust. Using EQ-5D values (instead of SF-6D scores) gives an ICER of £3,299 per QALY. Using NHS Reference Costs for surgical treatment (instead of local unit costs) gives an ICER of £5,708 per QALY.
Data sources				

J. Ratcliffe, J. E. Brazier, W. B. Campbell, S. Palfreyman, J. B. Macintyre, and J. A. Michaels. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. *Br.J.Surg.* 93 (2):182-186, 2006.
Health outcomes: This was taken from the results of the randomized controlled trial reported by Michaels et al. 2006[169]. **Quality-of-life weights:** SF-36 questionnaire scores at 1, 6, 12 and 24 months of follow-up were translated into preference-based SF-6D scores using the algorithm developed by Brazier et al. 2002[34]. EQ-5D scores were also considered. **Cost sources:** NHS Reference Costs and Personal Social Services Research Unit. Where national data was not available, local unit costs were obtained from the finance departments of two hospitals.
Comments
Source of funding: NHS R&D Health Technology Assessment (HTA) programme; **Limitations:** No decision analytic model was conducted to capture long-term costs and health outcomes. The short 2-year time horizon may underestimate the cost-effectiveness of surgical treatment as the clinical benefits of surgery including improvements in health-related quality of life would be expected to endure beyond 24 months. Including long-term costs and health outcomes may still give lower ICERs.
Overall applicability*: Directly applicable **Overall quality**:** Minor limitations

*Abbreviations: CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

†These results are also presented in Michaels 2006[170]

H.3 Chapter 9 – interventional treatment

Table 97: GOHEL2010

M. S. Gohel, D. M. Epstein, and A. H. Davies. Cost-effectiveness of traditional and endovenous treatments for varicose veins. *Br.J.Surg.* 97 (12):1815-1823, 2010.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision-analytic Markov model **Approach to analysis:** The model considers in the first 3 months the following outcomes: (1) initial intervention was successful and patient had no residual varicosities (2) veins were occluded but there remain residual varicosities, and (3) there is residual reflux or incomplete occlusion. Thereafter, the model considers the recurrence of vein reflux but not the recurrence of varicosities. **Perspective:** UK NHS	**Population:** Patients with unilateral symptomatic primary saphenous varicose veins **Cohort settings:** Start age = NR Male/Female = NR **Intervention 1:** Conservative care **Intervention 2:** Ultrasound-guided foam sclerotherapy **Intervention 3:** Endovenous laser ablation (local anaesthesia) **Intervention 4:** Radiofrequency ablation (local anaesthesia) **Intervention 5:** Surgery (day case) **Intervention 6**: Endovenous laser ablation (general anaesthesia) **Intervention 7:**	**Mean cost per patient:** Intervention 1: £0 Intervention 2: £429 Intervention 3: £1,031 Intervention 4: £1,110 Intervention 5: £1,242 Intervention 6: £1,915 Intervention 7: £1,964 Intervention 8: £2,000 **Currency & cost year:** 2008 UK pounds **Cost components incorporated:** Costs of catheter and generator, staff, ultrasonography, outpatient visits and sclerosant	**Primary outcome measure:** QALYs (mean per patient) Intervention 1: 3.522 QALYs Intervention 2: 3.836 QALYs Intervention 3: 3.940 QALYs Intervention 4: 3.944 QALYs Intervention 5: 3.951 QALYs Intervention 6: 3.954 QALYs Intervention 7: 3.951 QALYs Intervention 8: 3.954 QALYs	**ICERs** **Intervention 2 versus Intervention 1:** £1,366 per QALY gained (d/a) **Intervention 3 versus Intervention 2:** £5,799 per QALY gained (d/a) **Intervention 4 versus Intervention 3:** £17,350 per QALY gained (d/a) **Intervention 5 versus Intervention 4:** £19,012 per QALY gained (d/a) **Intervention 7 versus Intervention 5:** £100,451 per QALY gained (d/a) Intervention 6 was extendedly dominated and intervention 8 was dominated. Intervention 5 was the cost-effective strategy with a probability of 0.29. Intervention 3 had a probability of being the cost-effective option of 0.35, and Intervention 4 had a probability of 0.24. **Analysis of uncertainty:** One-way sensitivity analysis was conducted by varying: (1) the costs of treatments (2) estimates of relative treatment effectiveness with regards to saphenous vein reflux and residual varicosities and (3) the correlation

M. S. Gohel, D. M. Epstein, and A. H. Davies. Cost-effectiveness of traditional and endovenous treatments for varicose veins. ***Br.J.Surg.*** **97 (12):1815-1823, 2010.**				
Time horizon: 5 years **Treatment effect duration:** 5 years **Discounting:** Costs =3.5% ; Outcomes = 3.5%	Radiofrequency ablation (general anaesthesia) **Intervention 8:** Surgery (in patient)			between the risks of incomplete vein occlusion after treatment and residual varicosities. The results changed significantly from the base case in the following instances. If the odds ratio for re-intervention for residual varicosities after sequential versus concomitant phlebectomy was 5.50, radiofrequency ablation (under local anaesthesia) and endovenous laser ablation (under local anaesthesia) are equally likely to be cost effective and day-case surgery is dominated.
Data sources				
Health outcomes: Some outcomes were taken from clinical trials whilst other outcomes were informed by meta-analytic studies. The probability of complete/ successful occlusion following surgical ligation and stripping, for instance, was informed by the results of the clinical trial van den Bos et al. 2008 [275]; and the relative risks of retreatment for residual varicosities after sequential versus concomitant phlebectomy was taken from results of the randomized controlled study Carradice et al. 2009 [46]. The odds ratio of incomplete occlusion following stripping surgery versus sclerotherapy, on the other hand, was informed by the meta-analysis Wright et al. 2006 [286]. **Quality-of-life weights:** EQ5D-derived HRQoL scores and profile based on Rasmussen et al. 2007 [219], Rautio et al. 2002 [224] and Michaels et al. 2006 [170]. **Cost sources:** 2008-2009 UK NHS Reference costs, published drug and device manufacturer's list prices (for 2008-2009).				
Comments				
Source of funding: European Venous Forum Group, which is partly funded by the pharmaceutical industry; **Limitations:** Modelling was undertaken over a 5 year horizon, yet the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. All treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful.				
Overall applicability*: Directly applicable **Overall quality**:** Potentially serious limitations				

*Abbreviations: CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Appendix I: Forest plots

I.1 Chapter 7 – assessment for treatment

I.1.1 Diagnostic accuracy of hand held doppler

Figure 26: Diagnostic accuracy of hand held Doppler (threshold 0.5 seconds) vs. Duplex (threshold 1 second): Sapheno-femoral junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kent 1998	70	3	5	30	0.93 [0.85, 0.98]	0.91 [0.76, 0.98]
Kim 2000	36	9	1	24	0.97 [0.86, 1.00]	0.73 [0.54, 0.87]

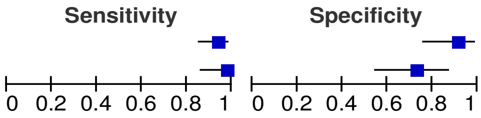


Figure 27: Diagnostic accuracy of hand held Doppler (threshold 1 second) vs. Duplex (threshold 1 second): Sapheno-femoral junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rautio 2002A	59	1	46	36	0.56 [0.46, 0.66]	0.97 [0.86, 1.00]
Rautio 2002B	31	1	17	13	0.65 [0.49, 0.78]	0.93 [0.66, 1.00]

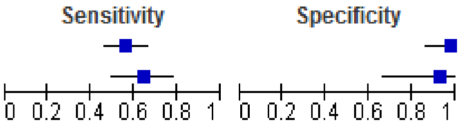


Figure 28: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 0.5 second): Sapheno-femoral junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Mercer 1998	43	2	16	28	0.73 [0.60, 0.84]	0.93 [0.78, 0.99]

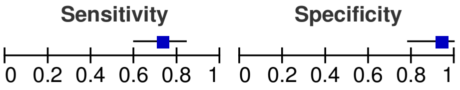


Figure 29: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Sapheno-femoral junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
DePalma 1993	24	5	26	25	0.48 [0.34, 0.63]	0.83 [0.65, 0.94]
Salaman 1995	49	1	4	18	0.92 [0.82, 0.98]	0.95 [0.74, 1.00]
Van der Heijden 1993	45	1	2	20	0.96 [0.85, 0.99]	0.95 [0.76, 1.00]

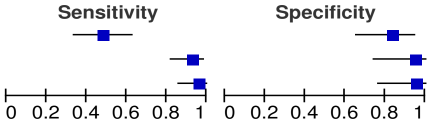


Figure 30: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 1 second): Sapheno-popliteal junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kent 1998	14	18	3	73	0.82 [0.57, 0.96]	0.80 [0.71, 0.88]

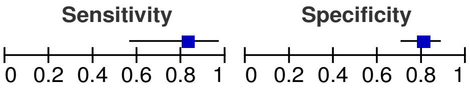


Figure 31: Diagnostic accuracy of hand held Doppler (threshold 1 second) vs. Duplex (threshold 1 second): Sapheno-popliteal junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rautio 2002A	3	4	10	95	0.23 [0.05, 0.54]	0.96 [0.90, 0.99]

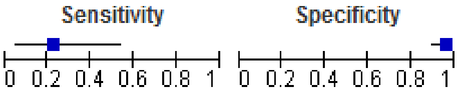


Figure 32: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 0.5 second): Sapheno-popliteal junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Mercer 1998	20	4	6	59	0.77 [0.56, 0.91]	0.94 [0.85, 0.98]

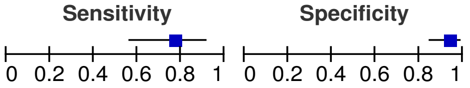


Figure 33: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Sapheno-popliteal junction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Salaman 1995	10	6	8	50	0.56 [0.31, 0.78]	0.89 [0.78, 0.96]
Van der Heijden 1993	17	0	0	51	1.00 [0.80, 1.00]	1.00 [0.93, 1.00]

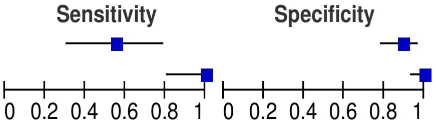


Figure 34: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 1 second): Great Saphenous Vein

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kent 1998	79	8	4	17	0.95 [0.88, 0.99]	0.68 [0.46, 0.85]

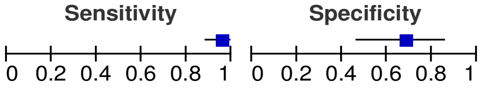


Figure 35: Diagnostic accuracy of hand held Doppler (threshold 1 second) vs. Duplex (threshold 1 second): Great Saphenous Vein

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rautio 2002A	54	8	39	41	0.58 [0.47, 0.68]	0.84 [0.70, 0.93]
Rautio 2002B	24	1	25	12	0.49 [0.34, 0.64]	0.92 [0.64, 1.00]

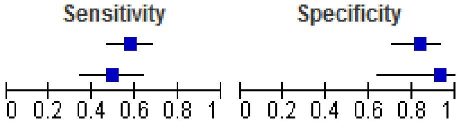


Figure 36: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Great Saphenous Vein

Study	TP	FP	FN	TN	Sensitivity	Specificity
Darke 1997	83	0	4	13	0.95 [0.89, 0.99]	1.00 [0.75, 1.00]
Van der Heijden 1993	41	1	4	22	0.91 [0.79, 0.98]	0.96 [0.78, 1.00]

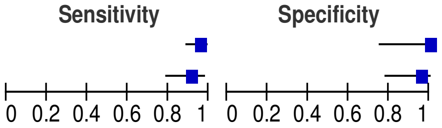


Figure 37: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Short Saphenous Vein

Study	TP	FP	FN	TN	Sensitivity	Specificity
Darke 1997	19	5	2	74	0.90 [0.70, 0.99]	0.94 [0.86, 0.98]
Van der Heijden 1993	16	0	2	50	0.89 [0.65, 0.99]	1.00 [0.93, 1.00]

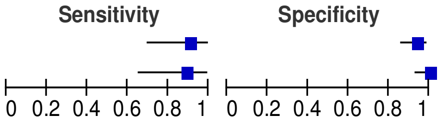


Figure 38: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 1 second): Perforators

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kent 1998	13	69	2	24	0.87 [0.60, 0.98]	0.26 [0.17, 0.36]

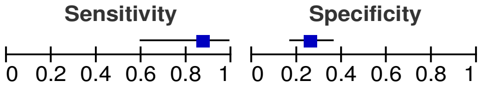


Figure 39: Diagnostic accuracy of hand held Doppler (threshold 0.5 second)vs. Duplex (threshold 0.5 second): Perforators

Study	TP	FP	FN	TN	Sensitivity	Specificity
Mercer 1998	18	8	17	46	0.51 [0.34, 0.69]	0.85 [0.73, 0.93]

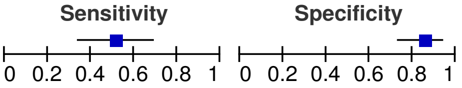


Figure 40: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Perforators

Study	TP	FP	FN	TN	Sensitivity	Specificity
Salaman 1995	2	13	5	54	0.29 [0.04, 0.71]	0.81 [0.69, 0.89]
Van der Heijden 1993	10	1	9	17	0.53 [0.29, 0.76]	0.94 [0.73, 1.00]

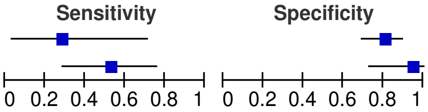


Figure 41: Diagnostic accuracy of hand held Doppler (threshold 0.5 second) vs. Duplex (threshold 1 second): Popliteal veins

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kent 1998	7	9	7	84	0.50 [0.23, 0.77]	0.90 [0.82, 0.95]

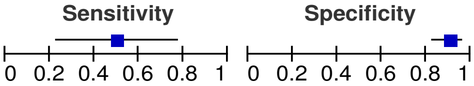


Figure 42: Diagnostic accuracy of hand held Doppler (threshold unknown) vs. Duplex (threshold unknown): Popliteal veins

Study	TP	FP	FN	TN	Sensitivity	Specificity
Salaman 1995	2	1	3	68	0.40 [0.05, 0.85]	0.99 [0.92, 1.00]

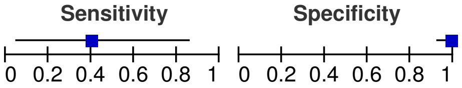
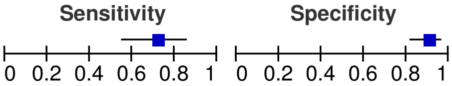


Figure 43: Diagnostic accuracy of hand held Doppler (threshold 1 second) vs. Duplex (threshold 1 second): Popliteal fossa

Study	TP	FP	FN	TN	Sensitivity	Specificity
Campbell 1997	28	8	11	74	0.72 [0.55, 0.85]	0.90 [0.82, 0.96]



I.1.2 Duplex assessment prior to interventional treatment

Figure 44: Duplex prior to treatment vs. no duplex: patient–assessed symptoms - Operated limbs unchanged or worse

	Duplex		No duplex			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.1.1 2 years						
Blomgren 2006A	15	130	19	120	100.0%	0.73 [0.39, 1.37]
Subtotal (95% CI)		**130**		**120**	**100.0%**	**0.73 [0.39, 1.37]**
Total events	15		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.32)						
1.1.2 7 years						
Blomgren 2011	16	123	28	108	100.0%	0.50 [0.29, 0.88]
Subtotal (95% CI)		**123**		**108**	**100.0%**	**0.50 [0.29, 0.88]**
Total events	16		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.43 (P = 0.02)						

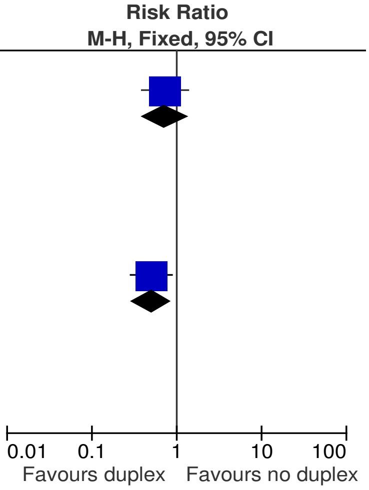


Figure 45: Duplex prior to treatment vs. no duplex: SFJ reflux

	Duplex		No duplex			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.2.1 6-8 weeks						
Blomgren 2005	10	160	37	166	97.4%	0.28 [0.14, 0.54]
Smith 2002	1	92	1	97	2.6%	1.05 [0.07, 16.61]
Subtotal (95% CI)		**252**		**263**	**100.0%**	**0.30 [0.16, 0.57]**
Total events	11		38			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 3.69 (P = 0.0002)						
1.2.2 2 years						
Blomgren 2005	14	127	44	129	100.0%	0.32 [0.19, 0.56]
Subtotal (95% CI)		**127**		**129**	**100.0%**	**0.32 [0.19, 0.56]**
Total events	14		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.03 (P < 0.0001)						
1.2.3 7 years						
Blomgren 2011	11	95	38	99	100.0%	0.30 [0.16, 0.55]
Subtotal (95% CI)		**95**		**99**	**100.0%**	**0.30 [0.16, 0.55]**
Total events	11		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.86 (P = 0.0001)						

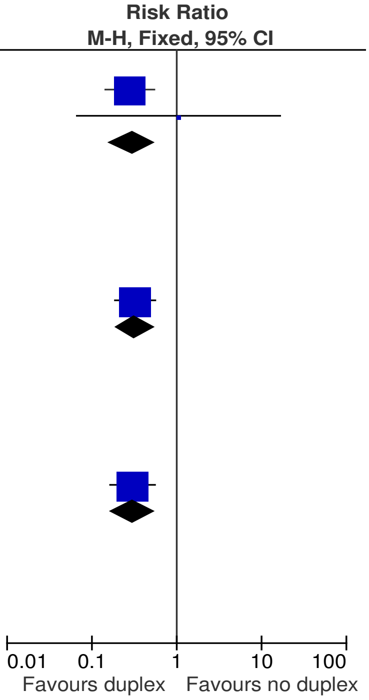


Figure 46: Duplex prior to treatment vs. no duplex: SPJ reflux

	Duplex		No duplex			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.3.1 8 weeks						
Blomgren 2005	4	160	9	166	100.0%	0.46 [0.14, 1.47]
Subtotal (95% CI)		**160**		**166**	**100.0%**	**0.46 [0.14, 1.47]**
Total events	4		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.3.2 2 years						
Blomgren 2005	7	127	13	129	100.0%	0.55 [0.23, 1.33]
Subtotal (95% CI)		**127**		**129**	**100.0%**	**0.55 [0.23, 1.33]**
Total events	7		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.3.3 7 years						
Blomgren 2011	2	95	9	99	100.0%	0.23 [0.05, 1.04]
Subtotal (95% CI)		**95**		**99**	**100.0%**	**0.23 [0.05, 1.04]**
Total events	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						

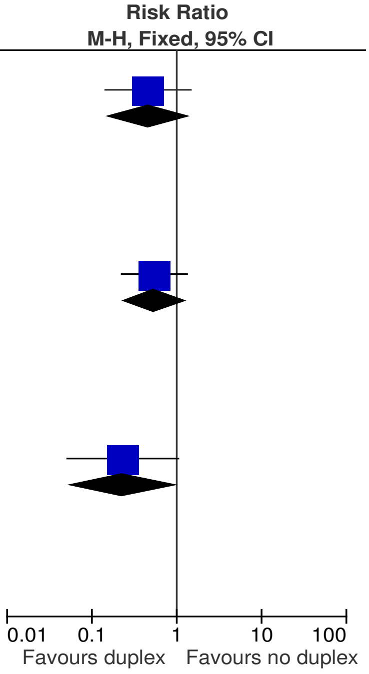


Figure 47: Duplex prior to treatment vs. no duplex: GSV reflux

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.4.1 12 months						
Smith 2002	8	92	9	97	100.0%	0.94 [0.38, 2.33]
Subtotal (95% CI)		**92**		**97**	**100.0%**	**0.94 [0.38, 2.33]**
Total events	8		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						

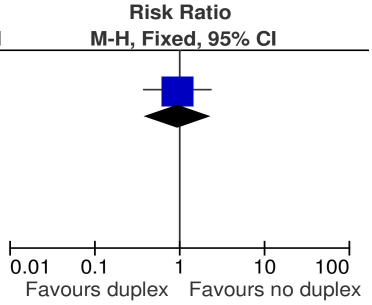


Figure 48: Duplex prior to treatment vs. no duplex: SSV reflux

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.5.1 6 weeks						
Smith 2002	4	92	6	97	100.0%	0.70 [0.20, 2.41]
Subtotal (95% CI)		**92**		**97**	**100.0%**	**0.70 [0.20, 2.41]**
Total events	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.5.2 12 months						
Smith 2002	6	92	8	97	100.0%	0.79 [0.29, 2.19]
Subtotal (95% CI)		**92**		**97**	**100.0%**	**0.79 [0.29, 2.19]**
Total events	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						

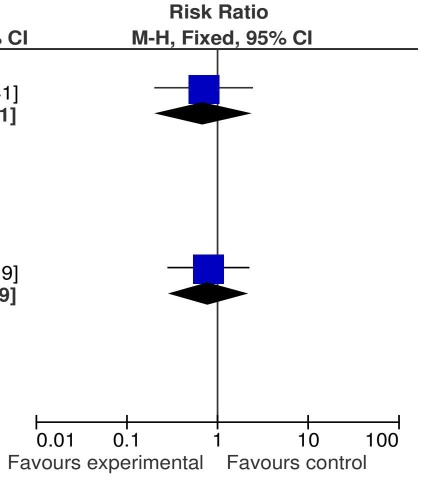


Figure 49: Duplex prior to treatment vs. no duplex: Perforators reflux

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.6.1 6 weeks						
Smith 2002	1	92	5	97	100.0%	0.21 [0.03, 1.77]
Subtotal (95% CI)		**92**		**97**	**100.0%**	**0.21 [0.03, 1.77]**
Total events	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.6.2 12 months						
Smith 2002	4	92	15	97	100.0%	0.28 [0.10, 0.82]
Subtotal (95% CI)		**92**		**97**	**100.0%**	**0.28 [0.10, 0.82]**
Total events	4		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.33 (P = 0.02)						

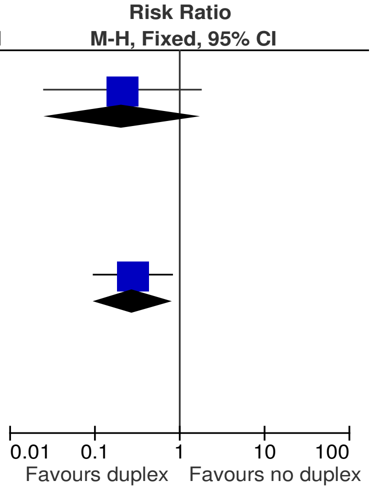


Figure 50: Duplex prior to treatment vs. no duplex: Development of new branch varicosities at 1 year

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Smith 2002	8	92	9	97	100.0%	0.94 [0.38, 2.33]
Total (95% CI)		**92**		**97**	**100.0%**	**0.94 [0.38, 2.33]**
Total events	8		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						

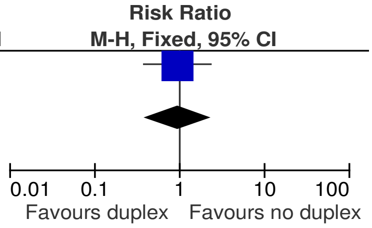


Figure 51: Duplex prior to treatment vs. no duplex: Need for, or actual, re-operation

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.8.1 2 years						
Blomgren 2005	3	145	14	147	100.0%	0.22 [0.06, 0.74]
Subtotal (95% CI)		**145**		**147**	**100.0%**	**0.22 [0.06, 0.74]**
Total events	3		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.44 (P = 0.01)						
1.8.2 7 years						
Blomgren 2011	15	124	38	134	100.0%	0.43 [0.25, 0.74]
Subtotal (95% CI)		**124**		**134**	**100.0%**	**0.43 [0.25, 0.74]**
Total events	15		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.06 (P = 0.002)						

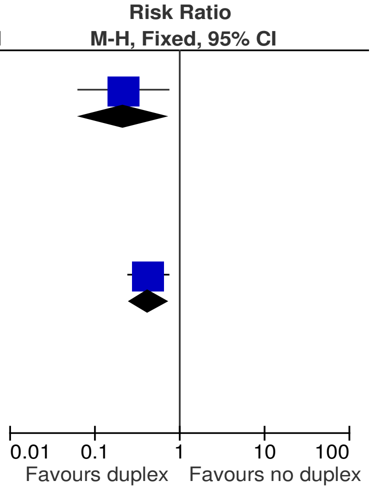


Figure 52: Duplex prior to treatment vs. no duplex: Adverse events - DVT

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Blomgren 2005	0	145	0	147		Not estimable
Total (95% CI)		**145**		**147**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

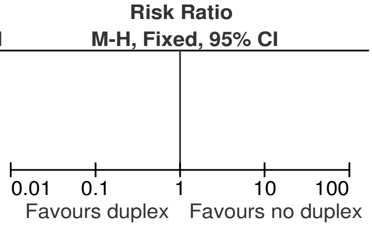


Figure 53: Duplex prior to treatment vs. no duplex: Complications of varicose veins at 7 years – venous ulcer

	Duplex		No duplex			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Blomgren 2011	0	70	0	88		Not estimable
Total (95% CI)		**70**		**88**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

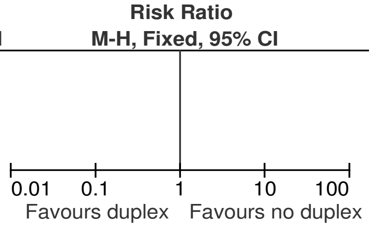
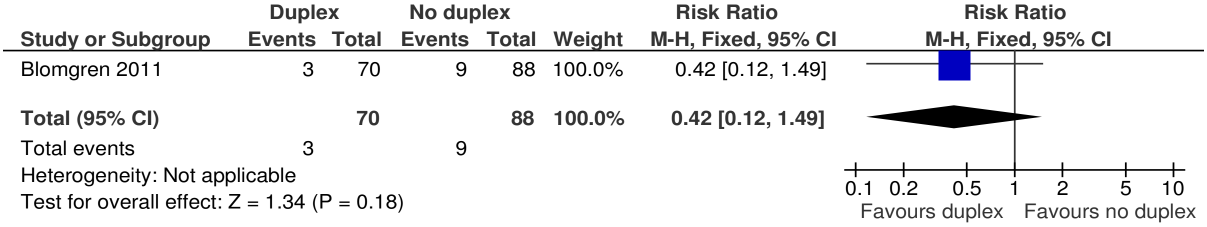


Figure 54: Duplex prior to treatment vs. no duplex: Complications of varicose veins at 7 years – pigmentation/eczema



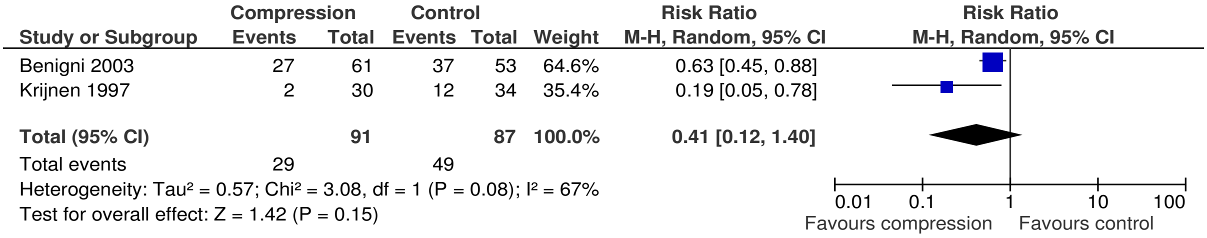
	Duplex		No duplex			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Blomgren 2011	3	70	9	88	100.0%	0.42 [0.12, 1.49]
Total (95% CI)		**70**		**88**	**100.0%**	**0.42 [0.12, 1.49]**
Total events	3		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

I.2 Chapter 8 – conservative management

I.2.1 Compression vs. no treatment/lifestyle advice

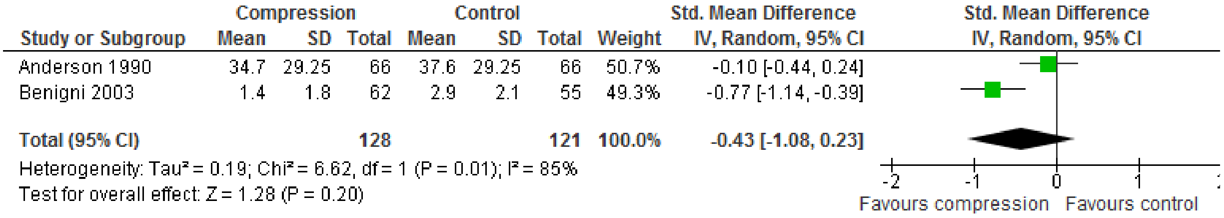
Figure 55: Compression vs. no treatment/lifestyle advice: numbers with pain or no improvement at end of treatment



	Compression		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Benigni 2003	27	61	37	53	64.6%	0.63 [0.45, 0.88]
Krijnen 1997	2	30	12	34	35.4%	0.19 [0.05, 0.78]
Total (95% CI)		**91**		**87**	**100.0%**	**0.41 [0.12, 1.40]**
Total events	29		49			

Heterogeneity: Tau² = 0.57; Chi² = 3.08, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.42 (P = 0.15)

Figure 56: Compression vs. no treatment/lifestyle advice: pain levels (VAS) at the end of treatment (better indicated by lower values). SMD used as scale of VAS unclear in both studies.



	Compression			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Anderson 1990	34.7	29.25	66	37.6	29.25	66	50.7%	-0.10 [-0.44, 0.24]
Benigni 2003	1.4	1.8	62	2.9	2.1	55	49.3%	-0.77 [-1.14, -0.39]
Total (95% CI)			**128**			**121**	**100.0%**	**-0.43 [-1.08, 0.23]**

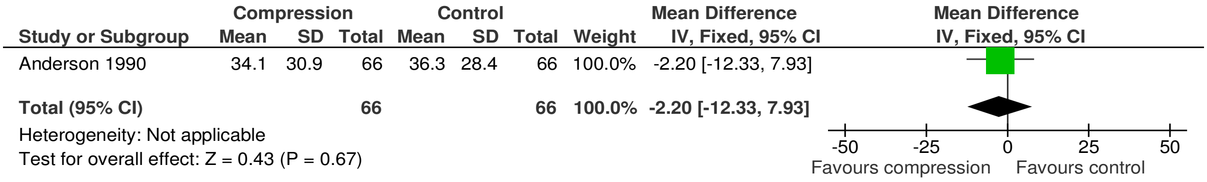
Heterogeneity: Tau² = 0.19; Chi² = 6.62, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 1.28 (P = 0.20)

Figure 57: Compression vs. no treatment/lifestyle advice: numbers with heavy or tired legs or no improvement in heavy or tired legs at end of treatment

	Compression		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Benigni 2003	20	59	35	54	68.4%	0.52 [0.35, 0.79]
Krijnen 1997	8	30	18	34	31.6%	0.50 [0.26, 0.99]
Total (95% CI)		**89**		**88**	**100.0%**	**0.52 [0.36, 0.73]**
Total events	28		53			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.70 (P = 0.0002)

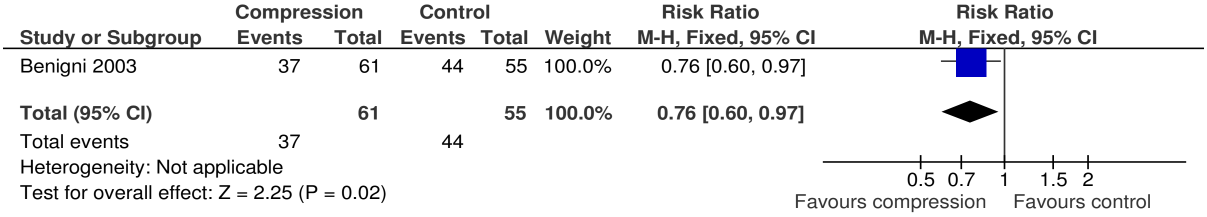
Figure 58: Compression vs. no treatment/lifestyle advice: heavy or tired legs (VAS) at end of treatment (better indicated by lower values)



	Compression			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Anderson 1990	34.1	30.9	66	36.3	28.4	66	100.0%	-2.20 [-12.33, 7.93]
Total (95% CI)			**66**			**66**	**100.0%**	**-2.20 [-12.33, 7.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

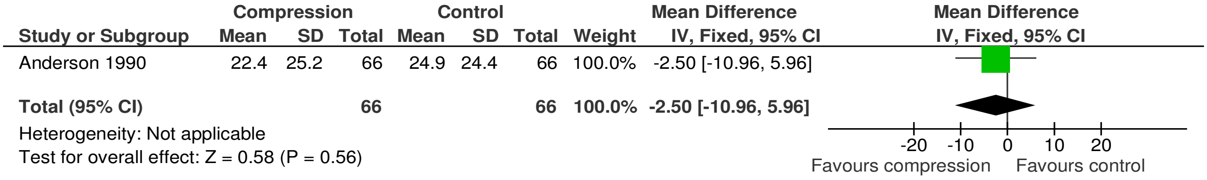
Figure 59: Compression vs. no treatment/lifestyle advice: numbers with no improvement in cramps at end of treatment



	Compression		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Benigni 2003	37	61	44	55	100.0%	0.76 [0.60, 0.97]
Total (95% CI)		**61**		**55**	**100.0%**	**0.76 [0.60, 0.97]**
Total events	37		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.25 (P = 0.02)

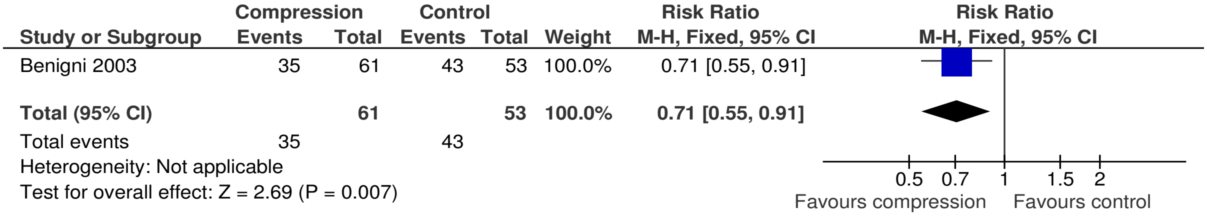
Figure 60: Compression vs. no treatment/lifestyle advice: night cramps level (VAS) at end of treatment (better indicated by lower values)



	Compression			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Anderson 1990	22.4	25.2	66	24.9	24.4	66	100.0%	-2.50 [-10.96, 5.96]
Total (95% CI)			**66**			**66**	**100.0%**	**-2.50 [-10.96, 5.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

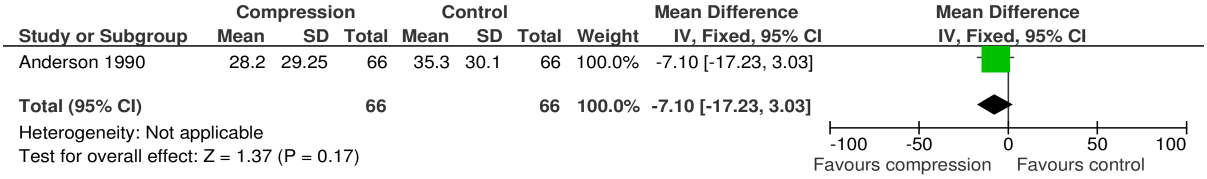
Figure 61: Compression vs. no treatment/lifestyle advice: numbers of patients reporting no improvement in ankle swelling at end of treatment



	Compression		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Benigni 2003	35	61	43	53	100.0%	0.71 [0.55, 0.91]
Total (95% CI)		**61**		**53**	**100.0%**	**0.71 [0.55, 0.91]**
Total events	35		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)

Figure 62: Compression vs. no treatment/lifestyle advice: self-reported swelling levels (VAS) at end of treatment (better indicated by lower values)



	Compression			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Anderson 1990	28.2	29.25	66	35.3	30.1	66	100.0%	-7.10 [-17.23, 3.03]
Total (95% CI)			**66**			**66**	**100.0%**	**-7.10 [-17.23, 3.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)

Figure 63: Compression vs. no treatment/lifestyle advice body image dissatisfaction (VAS) at end of treatment (better indicated by lower values)

	Compression			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Anderson 1990	43.2	37.4	66	41.1	38.2	66	100.0%	2.10 [-10.80, 15.00]
Total (95% CI)			**66**			**66**	**100.0%**	**2.10 [-10.80, 15.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

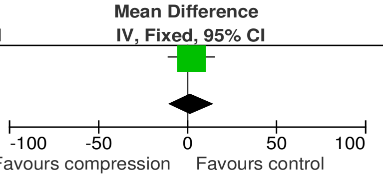
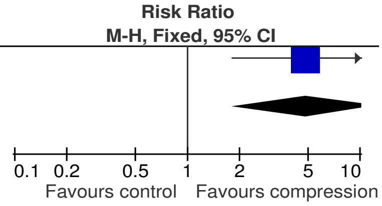


Figure 64: Compression vs. no treatment/lifestyle advice: numbers reporting fewer complaints

	compression		control			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Krijnen 1997	17	30	4	34	100.0%	4.82 [1.82, 12.73]	1997
Total (95% CI)		**30**		**34**	**100.0%**	**4.82 [1.82, 12.73]**	
Total events	17		4				

Heterogeneity: Not applicable
Test for overall effect: Z = 3.17 (P = 0.002)



I.2.2 Compression vs. interventional treatment

I.2.2.1 Compression vs. surgery

Figure 65: Compression vs. surgery: quality of life (higher score indicates better outcome)

	Surgery			Compression				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**Year**
1.5.1 SF-6D 1 year									
Micheals 2006A	0.77	0.1	75	0.73	0.11	98	100.0%	0.04 [0.01, 0.07]	2006
Subtotal (95% CI)			**75**			**98**	**100.0%**	**0.04 [0.01, 0.07]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.50 (P = 0.01)									
1.5.2 SF-6D 2 years									
Micheals 2006A	0.78	0.1	44	0.72	0.13	47	100.0%	0.06 [0.01, 0.11]	2006
Subtotal (95% CI)			**44**			**47**	**100.0%**	**0.06 [0.01, 0.11]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.48 (P = 0.01)									
1.5.3 EQ-5D 1 year									
Micheals 2006A	0.87	0.14	78	0.78	0.18	101	100.0%	0.09 [0.04, 0.14]	2006
Subtotal (95% CI)			**78**			**101**	**100.0%**	**0.09 [0.04, 0.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.76 (P = 0.0002)									
1.5.4 EQ-5D 2 years									
Micheals 2006A	0.84	0.21	34	0.85	0.17	44	100.0%	-0.01 [-0.10, 0.08]	2006
Subtotal (95% CI)			**34**			**44**	**100.0%**	**-0.01 [-0.10, 0.08]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.23 (P = 0.82)									

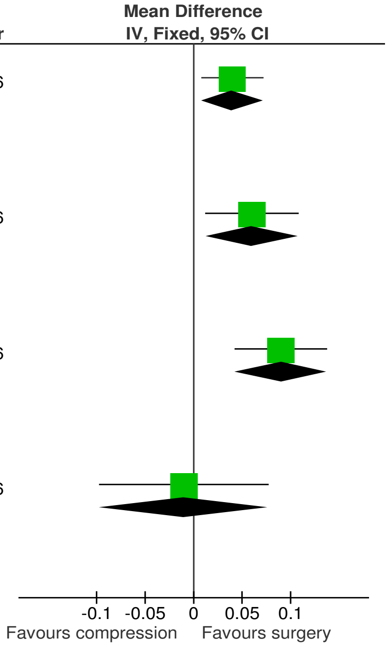


Figure 66: Compression vs. surgery: Patient assessed symptoms (proportion the same or worse)

	Compression		Surgery			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.6.1 aching at 1 yr						
Micheals 2006A	72	97	15	75	100.0%	3.71 [2.33, 5.92]
Subtotal (95% CI)		**97**		**75**	**100.0%**	**3.71 [2.33, 5.92]**
Total events	72		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.50 (P < 0.00001)						
1.6.2 heaviness at 1 year						
Micheals 2006A	52	97	9	75	100.0%	4.47 [2.36, 8.47]
Subtotal (95% CI)		**97**		**75**	**100.0%**	**4.47 [2.36, 8.47]**
Total events	52		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.58 (P < 0.00001)						
1.6.3 itching at 1 year						
Micheals 2006A	42	97	10	75	100.0%	3.25 [1.75, 6.04]
Subtotal (95% CI)		**97**		**75**	**100.0%**	**3.25 [1.75, 6.04]**
Total events	42		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.72 (P = 0.0002)						
1.6.4 swelling at 1 year						
Micheals 2006A	31	97	8	75	100.0%	3.00 [1.46, 6.13]
Subtotal (95% CI)		**97**		**75**	**100.0%**	**3.00 [1.46, 6.13]**
Total events	31		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.6.5 cosmetic concerns at 1 year						
Micheals 2006A	75	97	13	75	100.0%	4.46 [2.69, 7.40]
Subtotal (95% CI)		**97**		**75**	**100.0%**	**4.46 [2.69, 7.40]**
Total events	75		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.79 (P < 0.00001)						

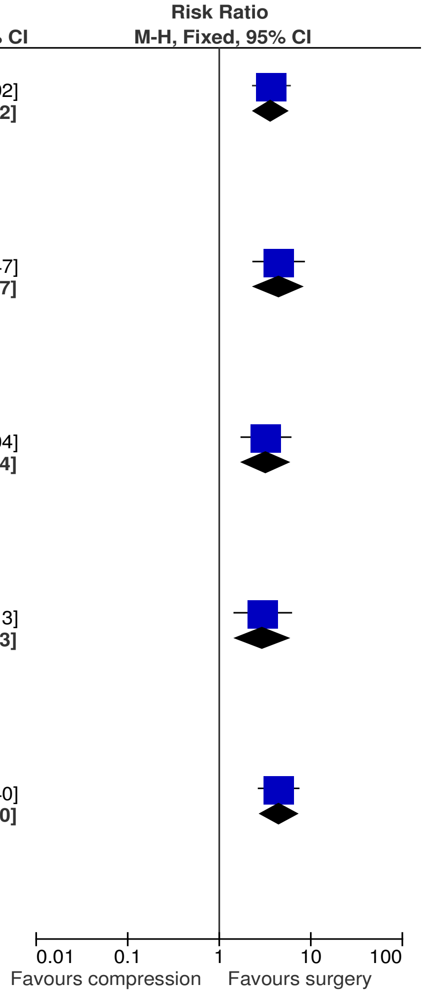


Figure 67: Compression vs. surgery: Adverse events – neural injury/damage

	Favours compression		surgery			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Micheals 2006A	0	122	1	124	100.0%	0.34 [0.01, 8.24]
Total (95% CI)		**122**		**124**	**100.0%**	**0.34 [0.01, 8.24]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						

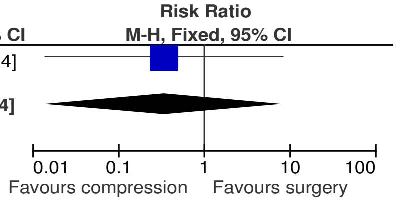
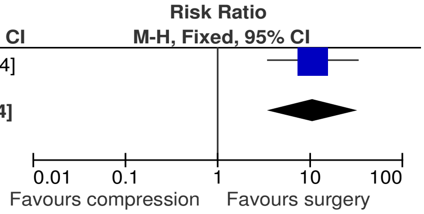


Figure 68: Compression vs. surgery: Patient dissatisfaction at 1 year

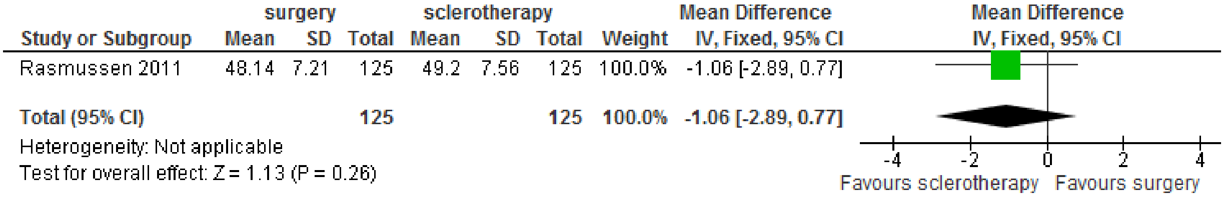
	compression		surgery			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Micheals 2006A	53	107	3	65	100.0%	10.73 [3.50, 32.94]
Total (95% CI)		**107**		**65**	**100.0%**	**10.73 [3.50, 32.94]**
Total events	53		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.15 (P < 0.0001)						



I.3 Chapter 9 – interventional treatment

I.3.1 Stripping surgery vs. foam sclerotherapy

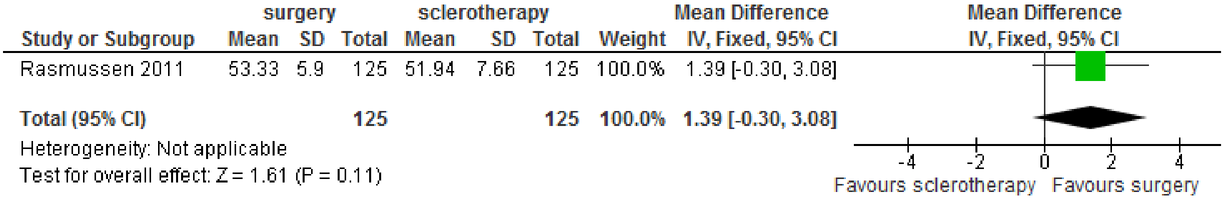
Figure 69: Stripping surgery vs. foam sclerotherapy:SF-36 Physical 4 weeks



	surgery			sclerotherapy				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rasmussen 2011	48.14	7.21	125	49.2	7.56	125	100.0%	-1.06 [-2.89, 0.77]	
Total (95% CI)			**125**			**125**	**100.0%**	**-1.06 [-2.89, 0.77]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

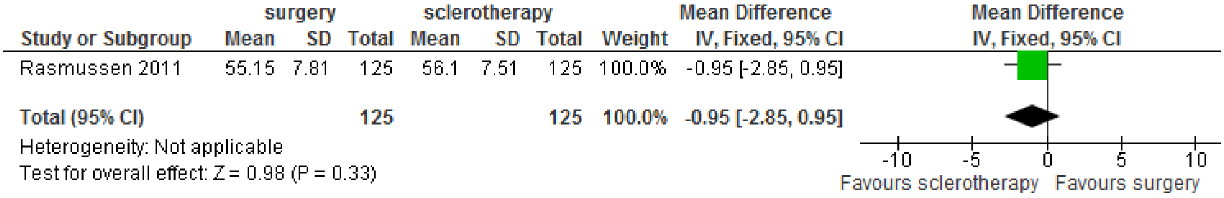
Figure 70: Stripping surgery vs. foam sclerotherapy:SF-36 Physical 1 year



	surgery			sclerotherapy				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rasmussen 2011	53.33	5.9	125	51.94	7.66	125	100.0%	1.39 [-0.30, 3.08]	
Total (95% CI)			**125**			**125**	**100.0%**	**1.39 [-0.30, 3.08]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)

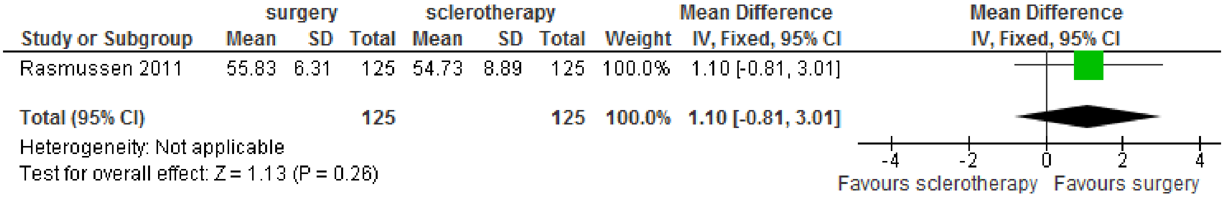
Figure 71: Stripping surgery vs. foam sclerotherapy: SF-36 mental 4 weeks



	surgery			sclerotherapy				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rasmussen 2011	55.15	7.81	125	56.1	7.51	125	100.0%	-0.95 [-2.85, 0.95]	
Total (95% CI)			**125**			**125**	**100.0%**	**-0.95 [-2.85, 0.95]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

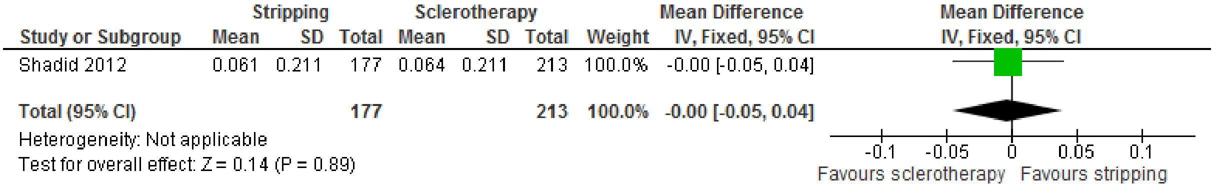
Figure 72: Stripping surgery vs. foam sclerotherapy: SF-36 mental 1 year



	surgery			sclerotherapy				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rasmussen 2011	55.83	6.31	125	54.73	8.89	125	100.0%	1.10 [-0.81, 3.01]	
Total (95% CI)			**125**			**125**	**100.0%**	**1.10 [-0.81, 3.01]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

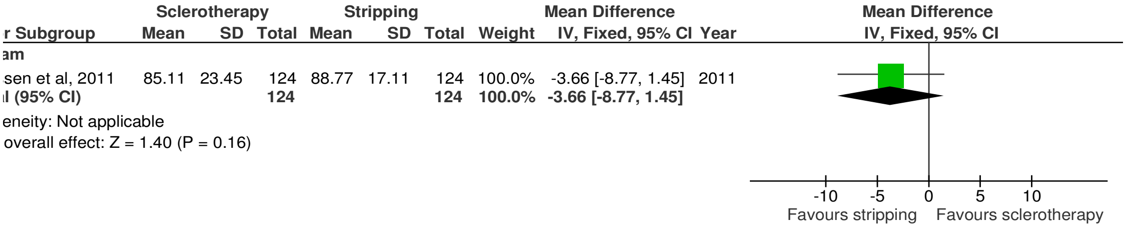
Figure 73: Stripping surgery vs. foam sclerotherapy: Patient- assessed outcomes: EQ-5D change from baseline to 2 years (higher better)



	Stripping			Sclerotherapy				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shadid 2012	0.061	0.211	177	0.064	0.211	213	100.0%	-0.00 [-0.05, 0.04]	
Total (95% CI)			**177**			**213**	**100.0%**	**-0.00 [-0.05, 0.04]**	

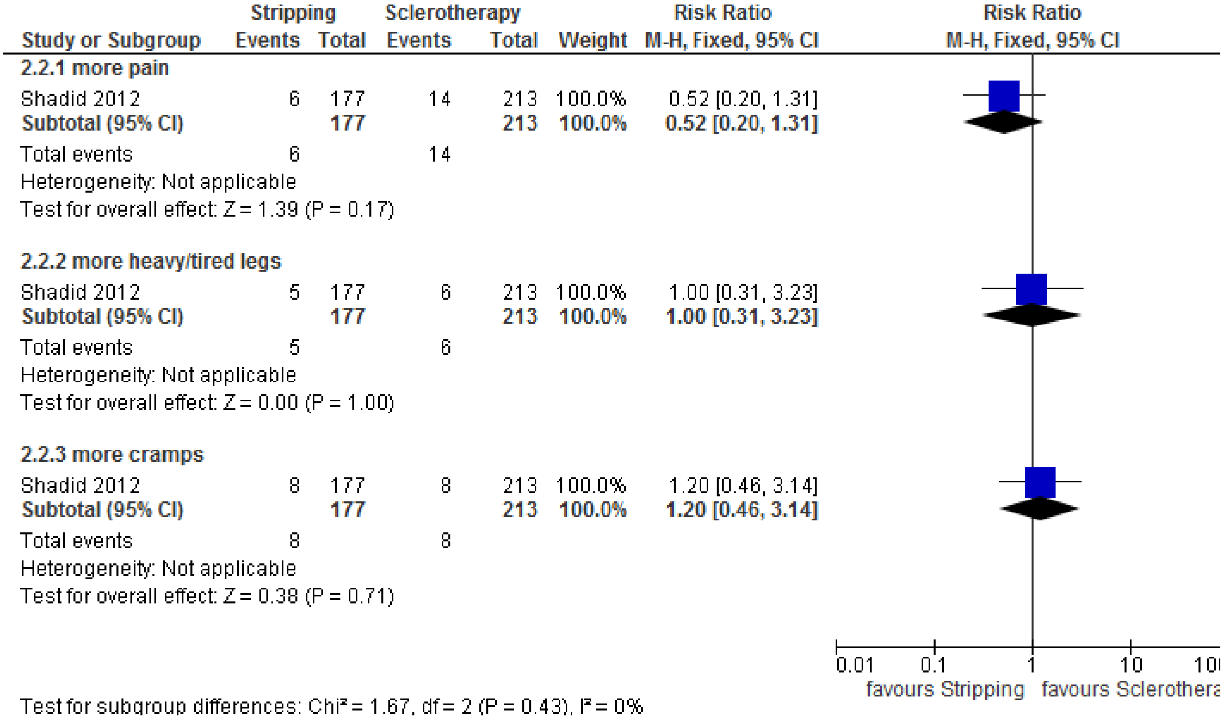
Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

Figure 74: Stripping surgery vs. foam sclerotherapy: Patient-assessed symptoms: Pain due to varicose veins (subscale from SF-36)



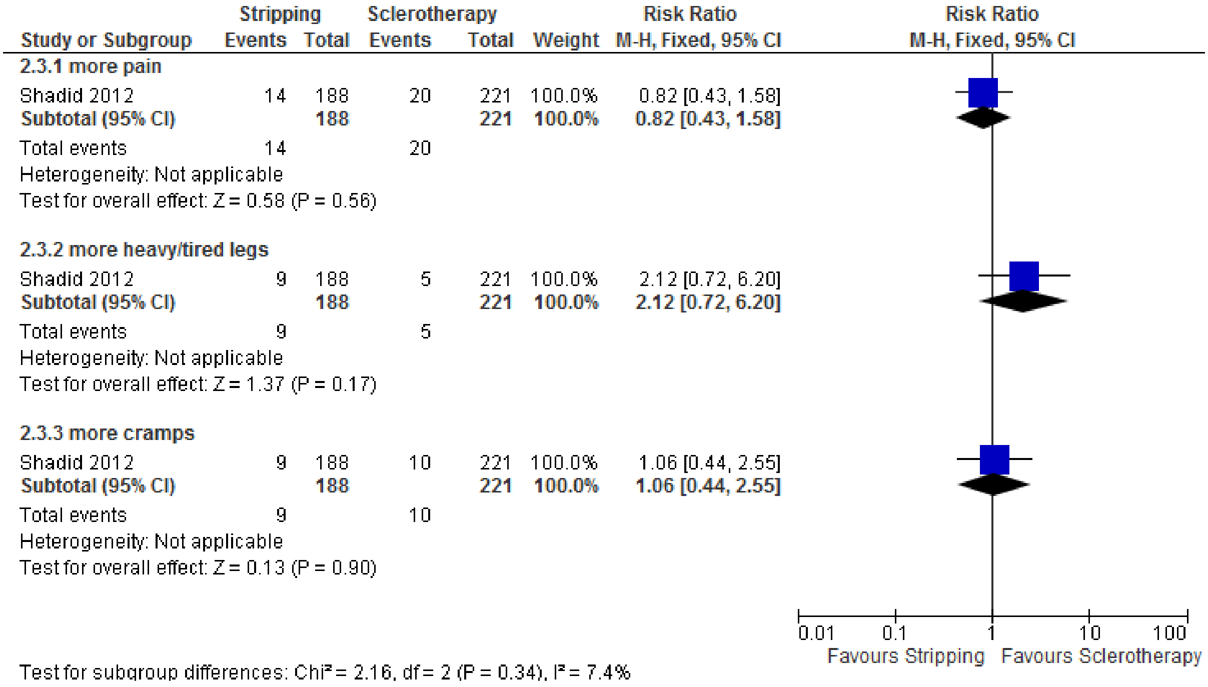
	Sclerotherapy			Stripping				Mean Difference	
r Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
am									
sen et al, 2011	85.11	23.45	124	88.77	17.11	124	100.0%	-3.66 [-8.77, 1.45]	2011
l (95% CI)			**124**			**124**	**100.0%**	**-3.66 [-8.77, 1.45]**	
eneity: Not applicable									
overall effect: Z = 1.40 (P = 0.16)									

Figure 75: Stripping surgery vs. foam sclerotherapy: Patient-assessed symptoms: worsening of symptoms at 2 years



	Stripping		Sclerotherapy			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
2.2.1 more pain						
Shadid 2012	6	177	14	213	100.0%	0.52 [0.20, 1.31]
Subtotal (95% CI)		**177**		**213**	**100.0%**	**0.52 [0.20, 1.31]**
Total events	6		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.17)						
2.2.2 more heavy/tired legs						
Shadid 2012	5	177	6	213	100.0%	1.00 [0.31, 3.23]
Subtotal (95% CI)		**177**		**213**	**100.0%**	**1.00 [0.31, 3.23]**
Total events	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.2.3 more cramps						
Shadid 2012	8	177	8	213	100.0%	1.20 [0.46, 3.14]
Subtotal (95% CI)		**177**		**213**	**100.0%**	**1.20 [0.46, 3.14]**
Total events	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: Chi² = 1.67, df = 2 (P = 0.43), I² = 0%						

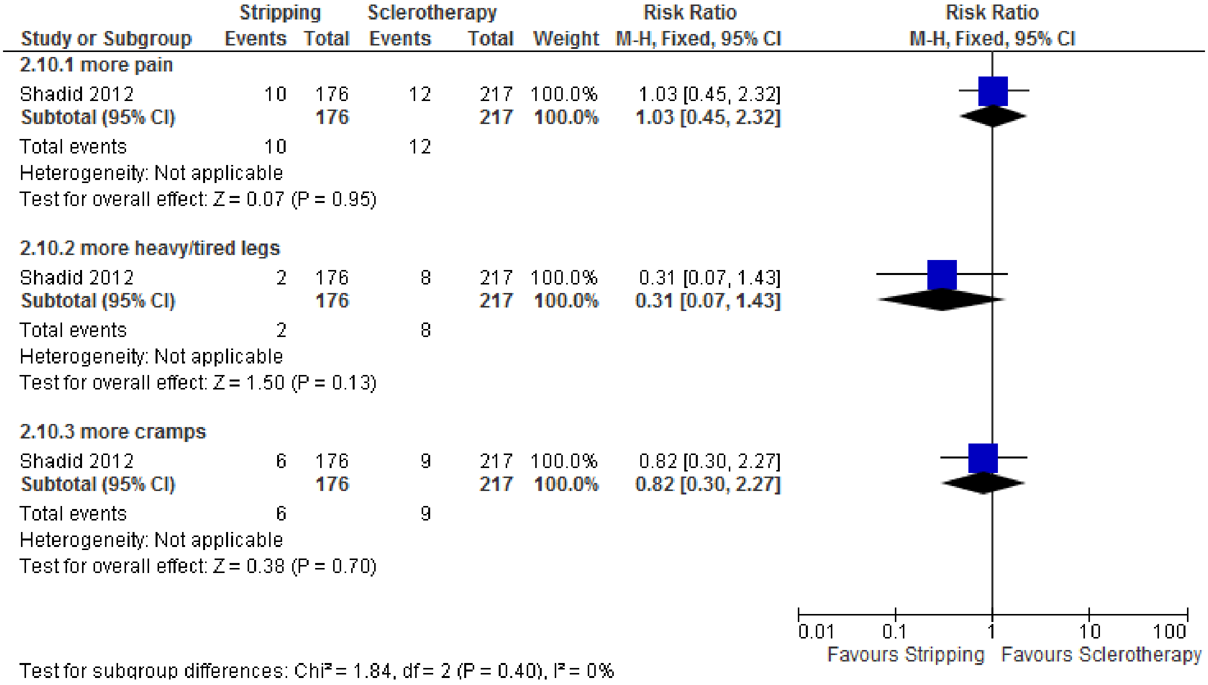
Figure 76: Stripping surgery vs. foam sclerotherapy: Patient-assessed symptoms: worsening of symptoms at 1 year



	Stripping		Sclerotherapy			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
2.3.1 more pain						
Shadid 2012	14	188	20	221	100.0%	0.82 [0.43, 1.58]
Subtotal (95% CI)		**188**		**221**	**100.0%**	**0.82 [0.43, 1.58]**
Total events	14		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.3.2 more heavy/tired legs						
Shadid 2012	9	188	5	221	100.0%	2.12 [0.72, 6.20]
Subtotal (95% CI)		**188**		**221**	**100.0%**	**2.12 [0.72, 6.20]**
Total events	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
2.3.3 more cramps						
Shadid 2012	9	188	10	221	100.0%	1.06 [0.44, 2.55]
Subtotal (95% CI)		**188**		**221**	**100.0%**	**1.06 [0.44, 2.55]**
Total events	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						

Test for subgroup differences: Chi² = 2.16, df = 2 (P = 0.34), I² = 7.4%

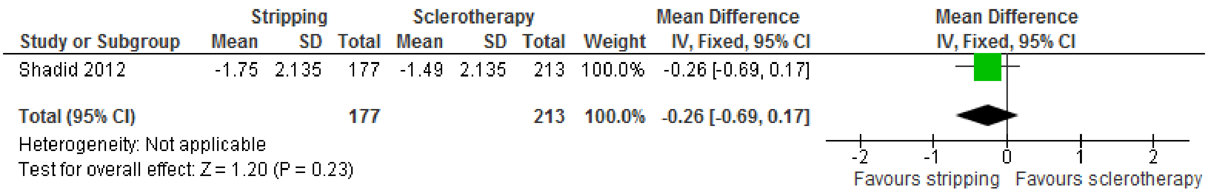
Figure 77: Stripping surgery vs. foam sclerotherapy: Patient-assessed symptoms: worsening of symptoms at 3 months



	Stripping		Sclerotherapy			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
2.10.1 more pain						
Shadid 2012	10	176	12	217	100.0%	1.03 [0.45, 2.32]
Subtotal (95% CI)		**176**		**217**	**100.0%**	**1.03 [0.45, 2.32]**
Total events	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.95)						
2.10.2 more heavy/tired legs						
Shadid 2012	2	176	8	217	100.0%	0.31 [0.07, 1.43]
Subtotal (95% CI)		**176**		**217**	**100.0%**	**0.31 [0.07, 1.43]**
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
2.10.3 more cramps						
Shadid 2012	6	176	9	217	100.0%	0.82 [0.30, 2.27]
Subtotal (95% CI)		**176**		**217**	**100.0%**	**0.82 [0.30, 2.27]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						

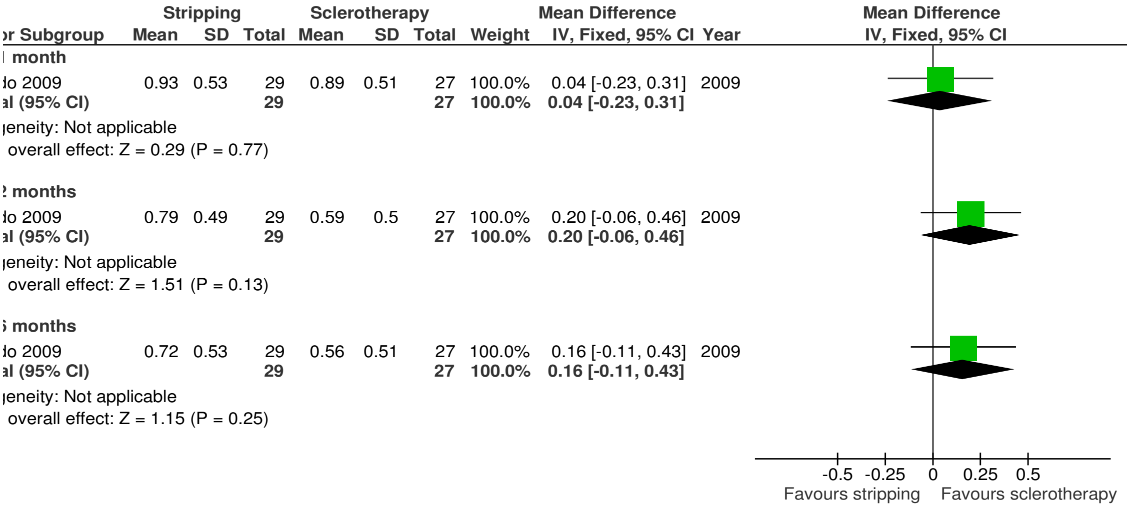
Test for subgroup differences: Chi² = 1.84, df = 2 (P = 0.40), I² = 0%

Figure 78: Stripping surgery vs. foam sclerotherapy: Physician-reported outcomes: overall VCSS score change from baseline by 2 years



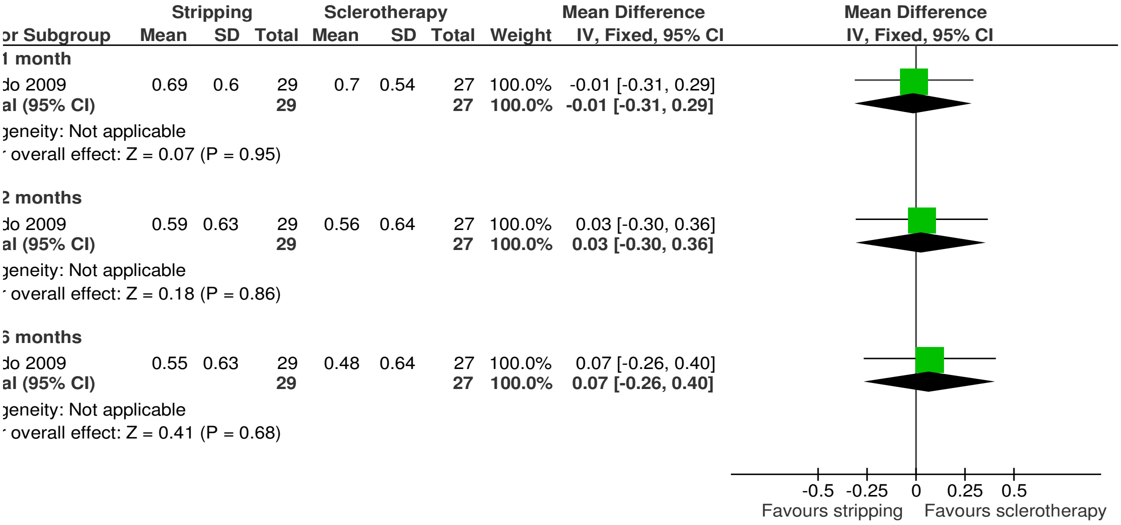
	Stripping			Sclerotherapy				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Shadid 2012	-1.75	2.135	177	-1.49	2.135	213	100.0%	-0.26 [-0.69, 0.17]
Total (95% CI)			**177**			**213**	**100.0%**	**-0.26 [-0.69, 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								

Figure 79: Stripping surgery vs. foam sclerotherapy: Physician-reported outcomes: VCSS pain



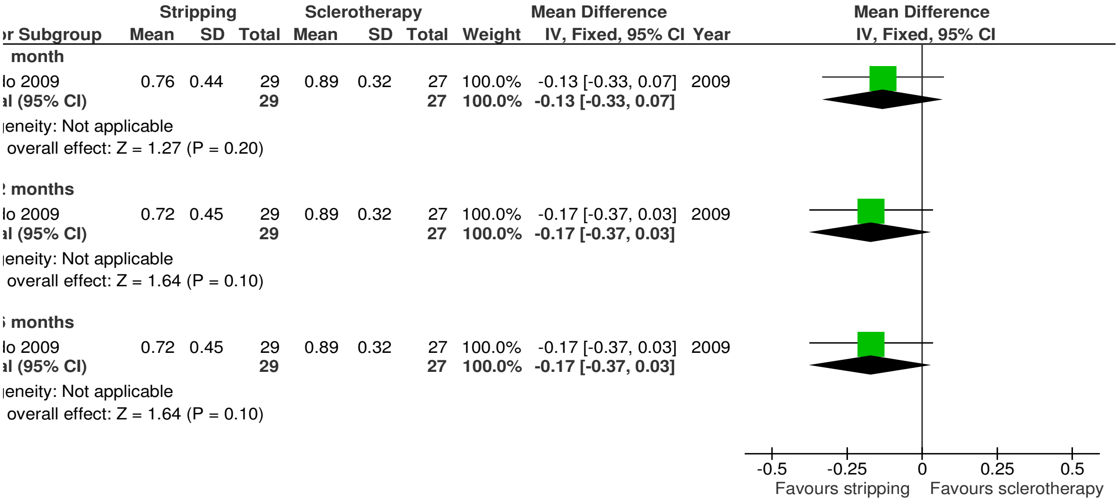
	Stripping			Sclerotherapy				Mean Difference	
r Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
month									
o 2009	0.93	0.53	29	0.89	0.51	27	100.0%	0.04 [-0.23, 0.31]	2009
l (95% CI)			**29**			**27**	**100.0%**	**0.04 [-0.23, 0.31]**	
eneity: Not applicable									
overall effect: Z = 0.29 (P = 0.77)									
months									
o 2009	0.79	0.49	29	0.59	0.5	27	100.0%	0.20 [-0.06, 0.46]	2009
l (95% CI)			**29**			**27**	**100.0%**	**0.20 [-0.06, 0.46]**	
eneity: Not applicable									
overall effect: Z = 1.51 (P = 0.13)									
months									
o 2009	0.72	0.53	29	0.56	0.51	27	100.0%	0.16 [-0.11, 0.43]	2009
l (95% CI)			**29**			**27**	**100.0%**	**0.16 [-0.11, 0.43]**	
eneity: Not applicable									
overall effect: Z = 1.15 (P = 0.25)									

Figure 80: Stripping surgery vs. foam sclerotherapy: Physician-reported outcomes: VCSS oedema



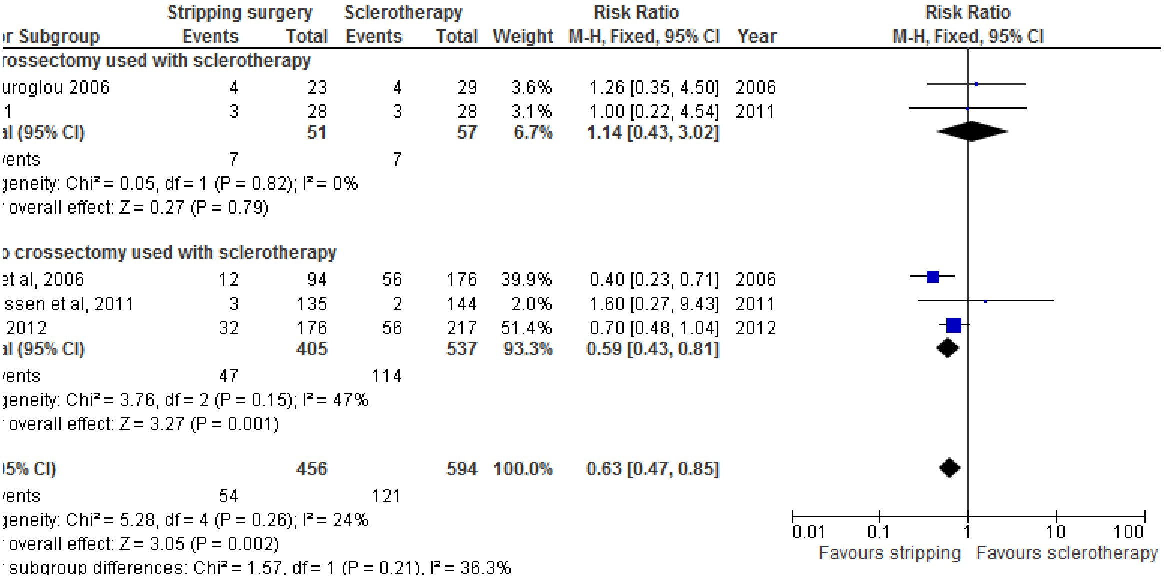
	Stripping			Sclerotherapy				Mean Difference
r Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
1 month								
o 2009	0.69	0.6	29	0.7	0.54	27	100.0%	-0.01 [-0.31, 0.29]
al (95% CI)			**29**			**27**	**100.0%**	**-0.01 [-0.31, 0.29]**
geneity: Not applicable								
overall effect: Z = 0.07 (P = 0.95)								
2 months								
o 2009	0.59	0.63	29	0.56	0.64	27	100.0%	0.03 [-0.30, 0.36]
al (95% CI)			**29**			**27**	**100.0%**	**0.03 [-0.30, 0.36]**
geneity: Not applicable								
overall effect: Z = 0.18 (P = 0.86)								
months								
o 2009	0.55	0.63	29	0.48	0.64	27	100.0%	0.07 [-0.26, 0.40]
al (95% CI)			**29**			**27**	**100.0%**	**0.07 [-0.26, 0.40]**
geneity: Not applicable								
overall effect: Z = 0.41 (P = 0.68)								

Figure 81: Stripping surgery vs. foam sclerotherapy: Physician-reported outcomes: VCSS inflammation



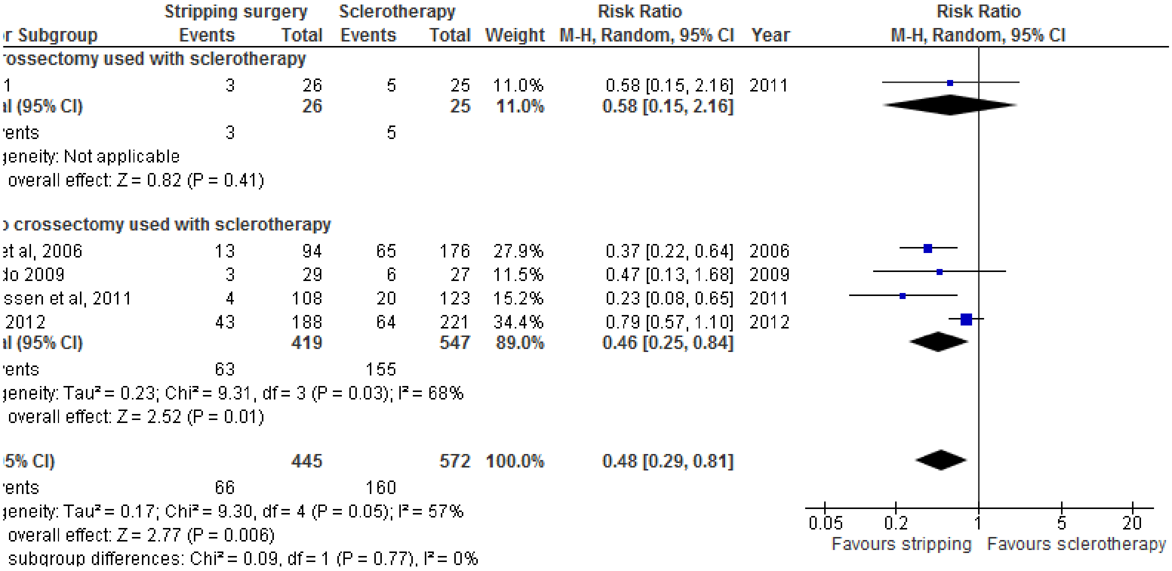
	Stripping			Sclerotherapy				Mean Difference	
r Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
month									
lo 2009	0.76	0.44	29	0.89	0.32	27	100.0%	-0.13 [-0.33, 0.07]	2009
l (95% CI)			**29**			**27**	**100.0%**	**-0.13 [-0.33, 0.07]**	
eneity: Not applicable									
overall effect: Z = 1.27 (P = 0.20)									
months									
lo 2009	0.72	0.45	29	0.89	0.32	27	100.0%	-0.17 [-0.37, 0.03]	2009
l (95% CI)			**29**			**27**	**100.0%**	**-0.17 [-0.37, 0.03]**	
eneity: Not applicable									
overall effect: Z = 1.64 (P = 0.10)									
months									
lo 2009	0.72	0.45	29	0.89	0.32	27	100.0%	-0.17 [-0.37, 0.03]	2009
l (95% CI)			**29**			**27**	**100.0%**	**-0.17 [-0.37, 0.03]**	
eneity: Not applicable									
overall effect: Z = 1.64 (P = 0.10)									

Figure 82: Stripping surgery vs. foam sclerotherapy: Presence of reflux within 3 months



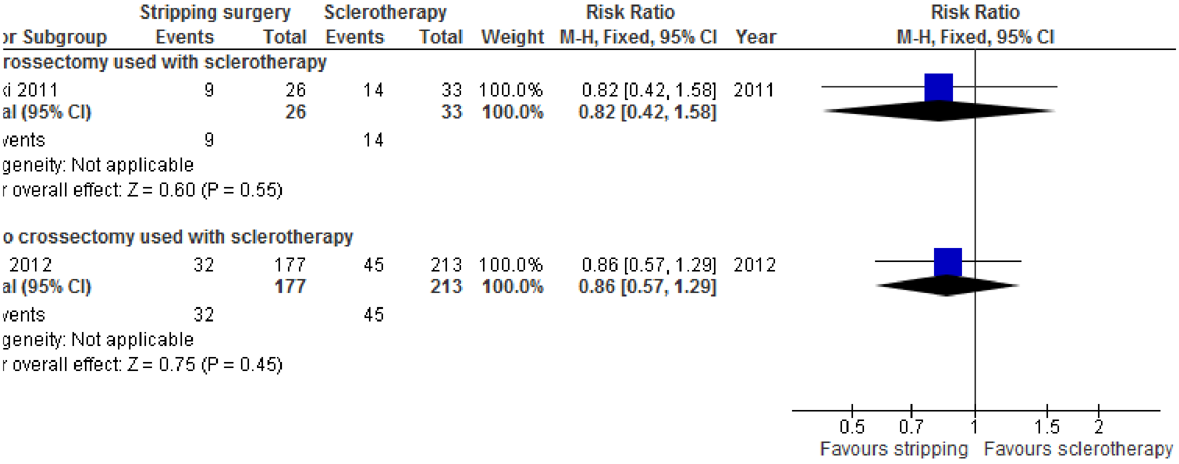
	Stripping surgery		Sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
rossectomy used with sclerotherapy							
uroglou 2006	4	23	4	29	3.6%	1.26 [0.35, 4.50]	2006
1	3	28	3	28	3.1%	1.00 [0.22, 4.54]	2011
l (95% CI)		**51**		**57**	**6.7%**	**1.14 [0.43, 3.02]**	
ents	7		7				
eneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 = 0%							
overall effect: Z = 0.27 (P = 0.79)							
o crossectomy used with sclerotherapy							
t al, 2006	12	94	56	176	39.9%	0.40 [0.23, 0.71]	2006
ssen et al, 2011	3	135	2	144	2.0%	1.60 [0.27, 9.43]	2011
2012	32	176	56	217	51.4%	0.70 [0.48, 1.04]	2012
l (95% CI)		**405**		**537**	**93.3%**	**0.59 [0.43, 0.81]**	
ents	47		114				
eneity: Chi^2 = 3.76, df = 2 (P = 0.15); I^2 = 47%							
overall effect: Z = 3.27 (P = 0.001)							
5% CI)		**456**		**594**	**100.0%**	**0.63 [0.47, 0.85]**	
ents	54		121				
eneity: Chi^2 = 5.28, df = 4 (P = 0.26); I^2 = 24%							
overall effect: Z = 3.05 (P = 0.002)							
subgroup differences: Chi^2 = 1.57, df = 1 (P = 0.21), I^2 = 36.3%							

Figure 83: Stripping surgery vs. foam sclerotherapy: Presence of reflux >3–12 months



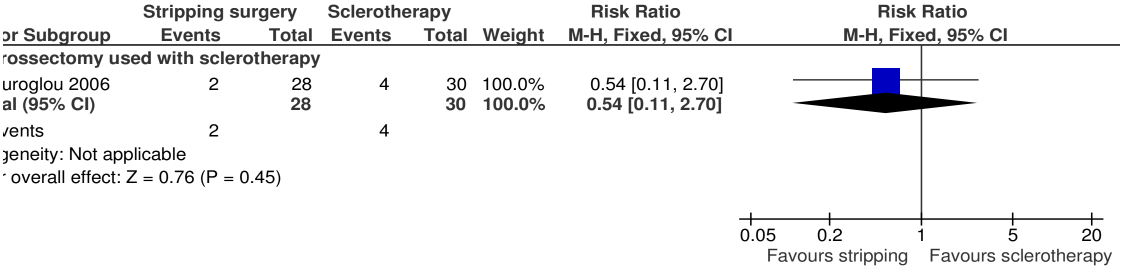
	Stripping surgery		Sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
ossectomy used with sclerotherapy							
1	3	26	5	25	11.0%	0.58 [0.15, 2.16]	2011
l (95% CI)		**26**		**25**	**11.0%**	**0.58 [0.15, 2.16]**	
ents	3		5				
jeneity: Not applicable							
overall effect: Z = 0.82 (P = 0.41)							
crossectomy used with sclerotherapy							
t al, 2006	13	94	65	176	27.9%	0.37 [0.22, 0.64]	2006
o 2009	3	29	6	27	11.5%	0.47 [0.13, 1.68]	2009
ssen et al, 2011	4	108	20	123	15.2%	0.23 [0.08, 0.65]	2011
2012	43	188	64	221	34.4%	0.79 [0.57, 1.10]	2012
l (95% CI)		**419**		**547**	**89.0%**	**0.46 [0.25, 0.84]**	
ents	63		155				
jeneity: Tau^2 = 0.23; Chi^2 = 9.31, df = 3 (P = 0.03); I^2 = 68%							
overall effect: Z = 2.52 (P = 0.01)							
5% CI)		**445**		**572**	**100.0%**	**0.48 [0.29, 0.81]**	
ents	66		160				
jeneity: Tau^2 = 0.17; Chi^2 = 9.30, df = 4 (P = 0.05); I^2 = 57%							
overall effect: Z = 2.77 (P = 0.006)							
subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.77), I^2 = 0%							

Figure 84: Stripping surgery vs. foam sclerotherapy: Presence of reflux >1-5 years



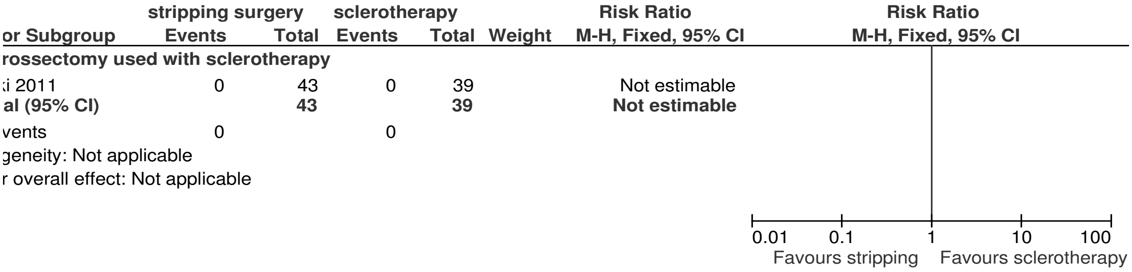
	Stripping surgery		Sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
rossectomy used with sclerotherapy							
i 2011	9	26	14	33	100.0%	0.82 [0.42, 1.58]	2011
al (95% CI)		**26**		**33**	**100.0%**	**0.82 [0.42, 1.58]**	
vents	9		14				
geneity: Not applicable							
r overall effect: Z = 0.60 (P = 0.55)							
o crossectomy used with sclerotherapy							
2012	32	177	45	213	100.0%	0.86 [0.57, 1.29]	2012
al (95% CI)		**177**		**213**	**100.0%**	**0.86 [0.57, 1.29]**	
vents	32		45				
geneity: Not applicable							
r overall effect: Z = 0.75 (P = 0.45)							

Figure 85: Stripping surgery vs. foam sclerotherapy: Need for further treatment from >3–12 months



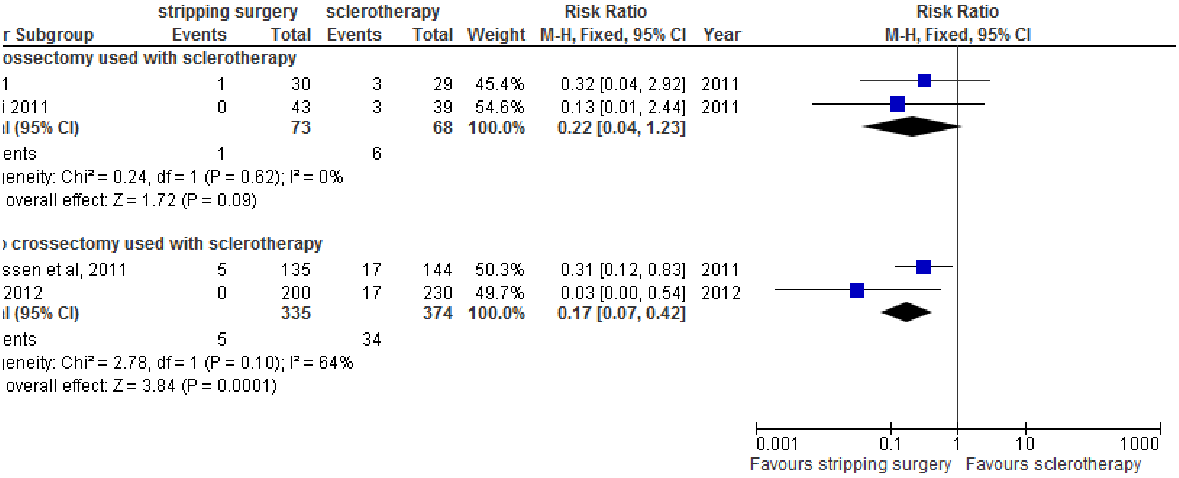
	Stripping surgery		Sclerotherapy			Risk Ratio
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
rossectomy used with sclerotherapy						
uroglou 2006	2	28	4	30	100.0%	0.54 [0.11, 2.70]
al (95% CI)		**28**		**30**	**100.0%**	**0.54 [0.11, 2.70]**
vents	2		4			
jeneity: Not applicable						
overall effect: Z = 0.76 (P = 0.45)						

Figure 86: Stripping surgery vs. foam sclerotherapy: Major neurological event



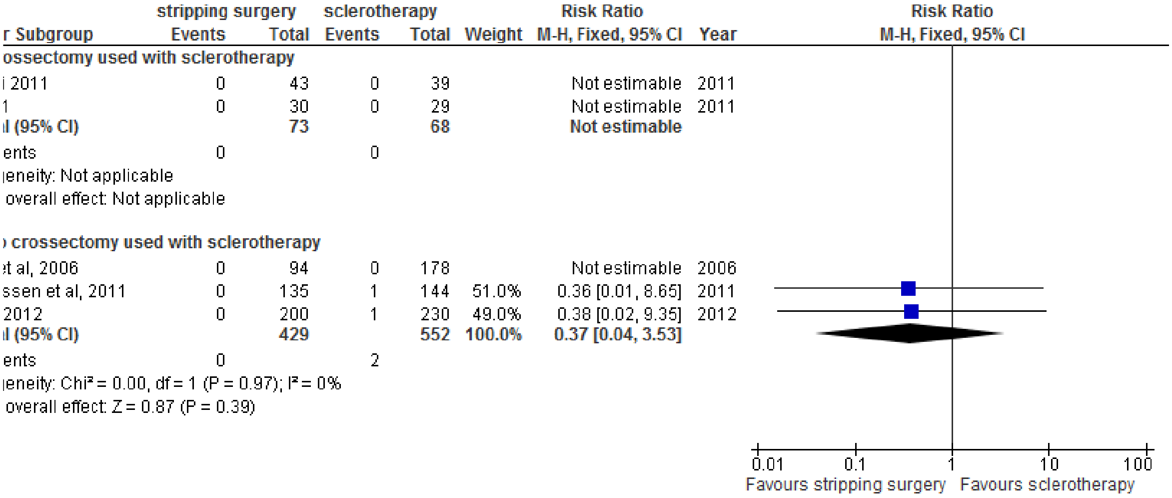
	stripping surgery		sclerotherapy			Risk Ratio
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
rossectomy used with sclerotherapy						
:i 2011	0	43	0	39		Not estimable
al (95% CI)		**43**		**39**		**Not estimable**
vents	0		0			
geneity: Not applicable						
r overall effect: Not applicable						

Figure 87: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Phlebitis



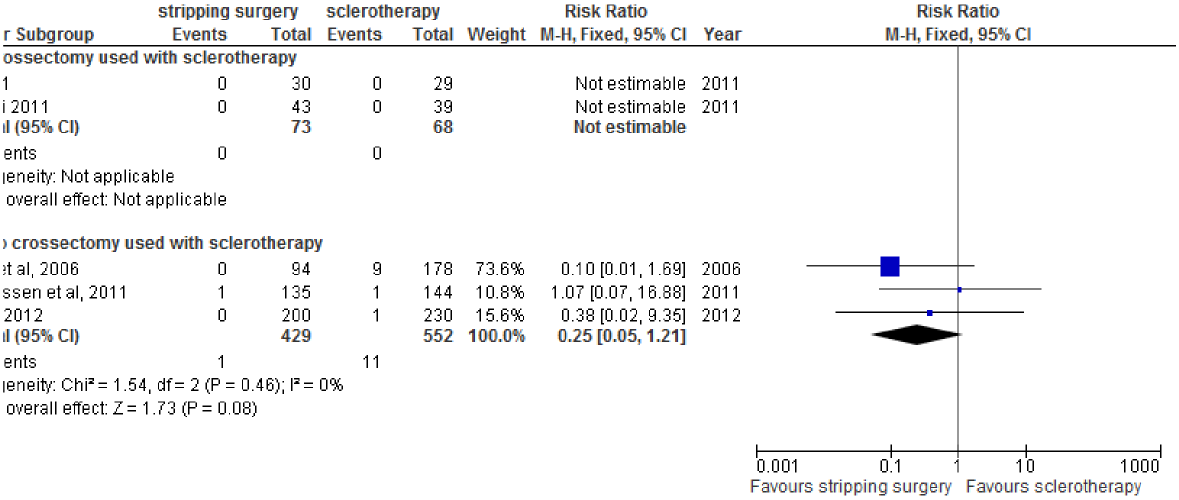
	stripping surgery		sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
ossectomy used with sclerotherapy							
1	1	30	3	29	45.4%	0.32 [0.04, 2.92]	2011
i 2011	0	43	3	39	54.6%	0.13 [0.01, 2.44]	2011
il (95% CI)		**73**		**68**	**100.0%**	**0.22 [0.04, 1.23]**	
ents	1		6				
ıeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%							
overall effect: Z = 1.72 (P = 0.09)							
› crossectomy used with sclerotherapy							
ssen et al, 2011	5	135	17	144	50.3%	0.31 [0.12, 0.83]	2011
2012	0	200	17	230	49.7%	0.03 [0.00, 0.54]	2012
il (95% CI)		**335**		**374**	**100.0%**	**0.17 [0.07, 0.42]**	
ents	5		34				
ıeneity: Chi² = 2.78, df = 1 (P = 0.10); I² = 64%							
overall effect: Z = 3.84 (P = 0.0001)							

Figure 88: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: PE



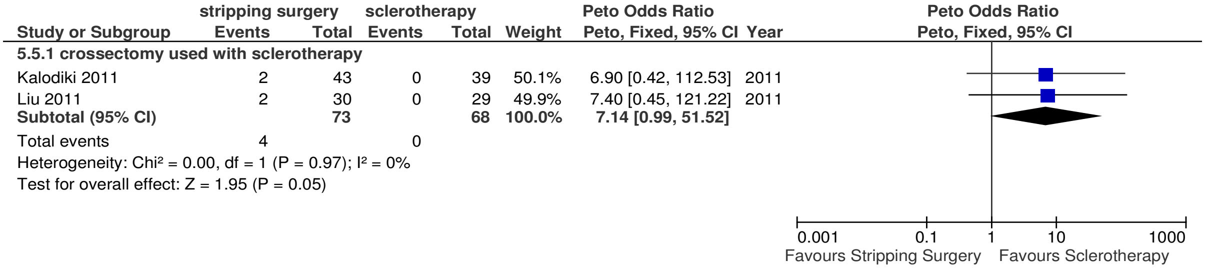
	stripping surgery		sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
ossectomy used with sclerotherapy							
i 2011	0	43	0	39		Not estimable	2011
1	0	30	0	29		Not estimable	2011
il (95% CI)		**73**		**68**		**Not estimable**	
ents	0		0				
ıeneity: Not applicable							
overall effect: Not applicable							
› crossectomy used with sclerotherapy							
ɛt al, 2006	0	94	0	178		Not estimable	2006
ssen et al, 2011	0	135	1	144	51.0%	0.36 [0.01, 8.65]	2011
2012	0	200	1	230	49.0%	0.38 [0.02, 9.35]	2012
il (95% CI)		**429**		**552**	**100.0%**	**0.37 [0.04, 3.53]**	
ents	0		2				
ıeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%							
overall effect: Z = 0.87 (P = 0.39)							

Figure 89: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: DVT



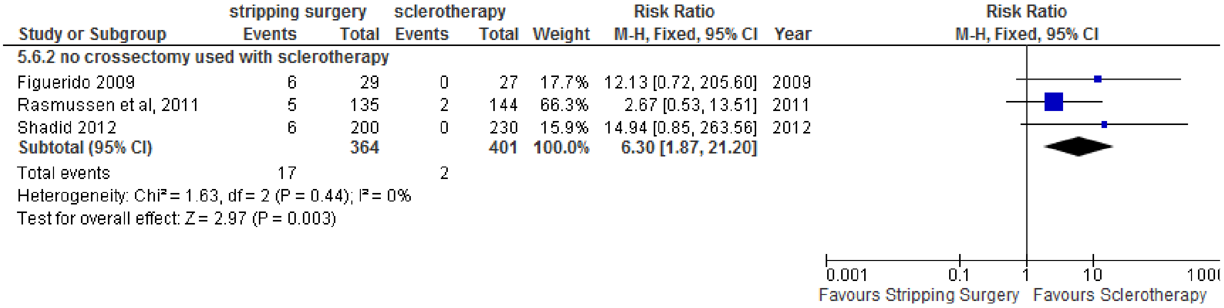
	stripping surgery		sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
ossectomy used with sclerotherapy							
1	0	30	0	29		Not estimable	2011
i 2011	0	43	0	39		Not estimable	2011
il (95% CI)		**73**		**68**		**Not estimable**	
ents	0		0				
jeneity: Not applicable							
overall effect: Not applicable							
› crossectomy used with sclerotherapy							
ɛt al, 2006	0	94	9	178	73.6%	0.10 [0.01, 1.69]	2006
ssen et al, 2011	1	135	1	144	10.8%	1.07 [0.07, 16.88]	2011
2012	0	200	1	230	15.6%	0.38 [0.02, 9.35]	2012
il (95% CI)		**429**		**552**	**100.0%**	**0.25 [0.05, 1.21]**	
ents	1		11				
jeneity: Chi² = 1.54, df = 2 (P = 0.46); I² = 0%							
overall effect: Z = 1.73 (P = 0.08)							

Figure 90: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Nerve injury/damage - with crossectomy



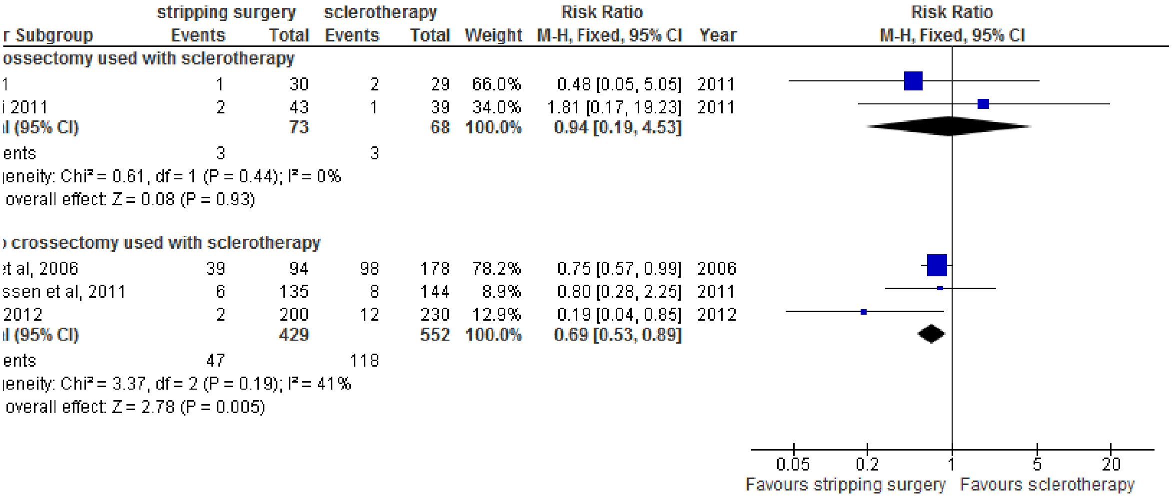
	stripping surgery		sclerotherapy			Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year
5.5.1 crossectomy used with sclerotherapy							
Kalodiki 2011	2	43	0	39	50.1%	6.90 [0.42, 112.53]	2011
Liu 2011	2	30	0	29	49.9%	7.40 [0.45, 121.22]	2011
Subtotal (95% CI)		**73**		**68**	**100.0%**	**7.14 [0.99, 51.52]**	
Total events	4		0				
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%							
Test for overall effect: Z = 1.95 (P = 0.05)							

Figure 91: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Nerve injury/damage - no crossectomy



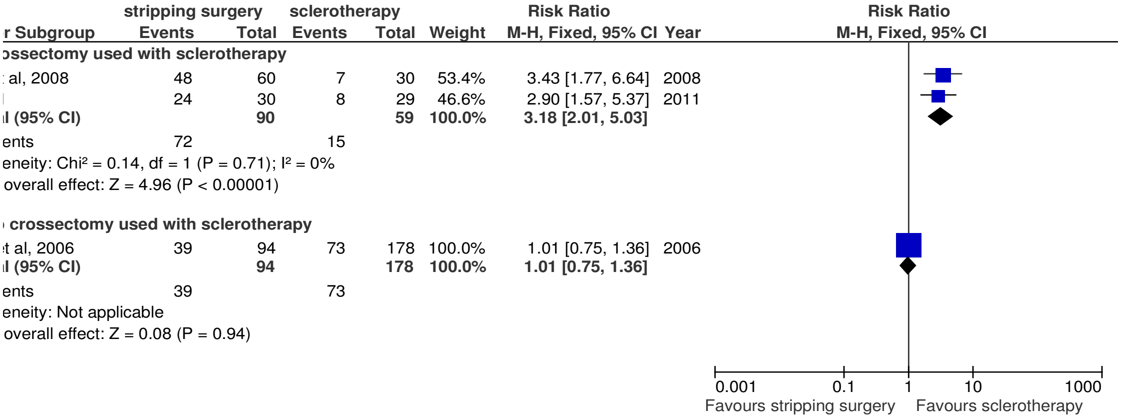
	stripping surgery		sclerotherapy			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
5.6.2 no crossectomy used with sclerotherapy							
Figuerido 2009	6	29	0	27	17.7%	12.13 [0.72, 205.60]	2009
Rasmussen et al, 2011	5	135	2	144	66.3%	2.67 [0.53, 13.51]	2011
Shadid 2012	6	200	0	230	15.9%	14.94 [0.85, 263.56]	2012
Subtotal (95% CI)		**364**		**401**	**100.0%**	**6.30 [1.87, 21.20]**	
Total events	17		2				
Heterogeneity: Chi² = 1.63, df = 2 (P = 0.44); I² = 0%							
Test for overall effect: Z = 2.97 (P = 0.003)							

Figure 92: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Skin discolouration/hyper pigmentation



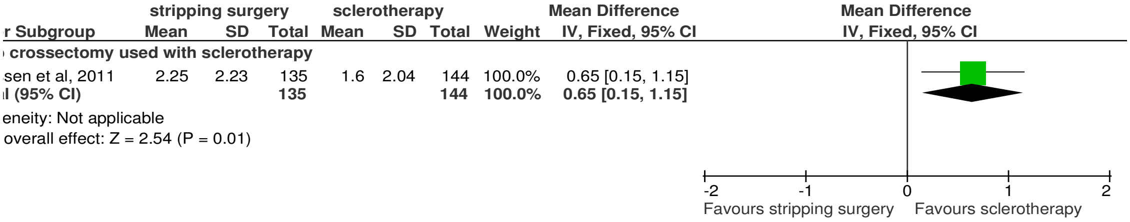
	stripping surgery		sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
ossectomy used with sclerotherapy							
1	1	30	2	29	66.0%	0.48 [0.05, 5.05]	2011
i 2011	2	43	1	39	34.0%	1.81 [0.17, 19.23]	2011
l (95% CI)		73		68	100.0%	0.94 [0.19, 4.53]	
ents	3		3				
jeneity: Chi² = 0.61, df = 1 (P = 0.44); I² = 0%							
overall effect: Z = 0.08 (P = 0.93)							
crossectomy used with sclerotherapy							
t al, 2006	39	94	98	178	78.2%	0.75 [0.57, 0.99]	2006
ssen et al, 2011	6	135	8	144	8.9%	0.80 [0.28, 2.25]	2011
2012	2	200	12	230	12.9%	0.19 [0.04, 0.85]	2012
l (95% CI)		429		552	100.0%	0.69 [0.53, 0.89]	
ents	47		118				
jeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%							
overall effect: Z = 2.78 (P = 0.005)							

Figure 93: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Post procedure pain



	stripping surgery		sclerotherapy			Risk Ratio	
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
ossectomy used with sclerotherapy							
al, 2008	48	60	7	30	53.4%	3.43 [1.77, 6.64]	2008
	24	30	8	29	46.6%	2.90 [1.57, 5.37]	2011
l (95% CI)		90		59	100.0%	3.18 [2.01, 5.03]	
ents	72		15				
eneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%							
overall effect: Z = 4.96 (P < 0.00001)							
crossectomy used with sclerotherapy							
t al, 2006	39	94	73	178	100.0%	1.01 [0.75, 1.36]	2006
l (95% CI)		94		178	100.0%	1.01 [0.75, 1.36]	
ents	39		73				
eneity: Not applicable							
overall effect: Z = 0.08 (P = 0.94)							

Figure 94: Stripping surgery vs. foam sclerotherapy: Adverse events from intervention: Post procedure pain VAS 1-10

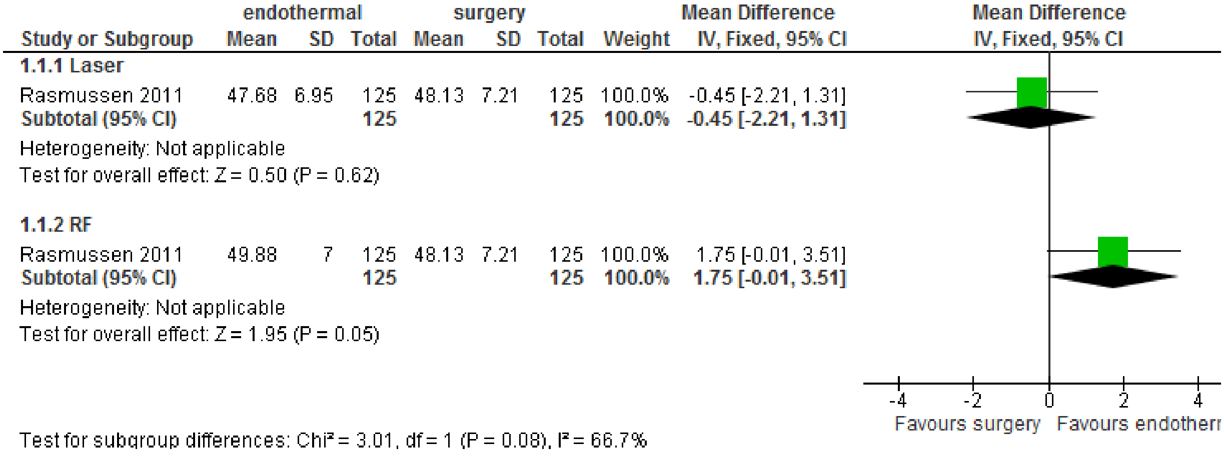


	stripping surgery			sclerotherapy				Mean Difference
r Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
crossectomy used with sclerotherapy								
sen et al, 2011	2.25	2.23	135	1.6	2.04	144	100.0%	0.65 [0.15, 1.15]
l (95% CI)			135			144	100.0%	0.65 [0.15, 1.15]
eneity: Not applicable								
overall effect: Z = 2.54 (P = 0.01)								

I.3.2 Stripping surgery vs. endothermal ablation

I.3.2.1 Primary varicose veins

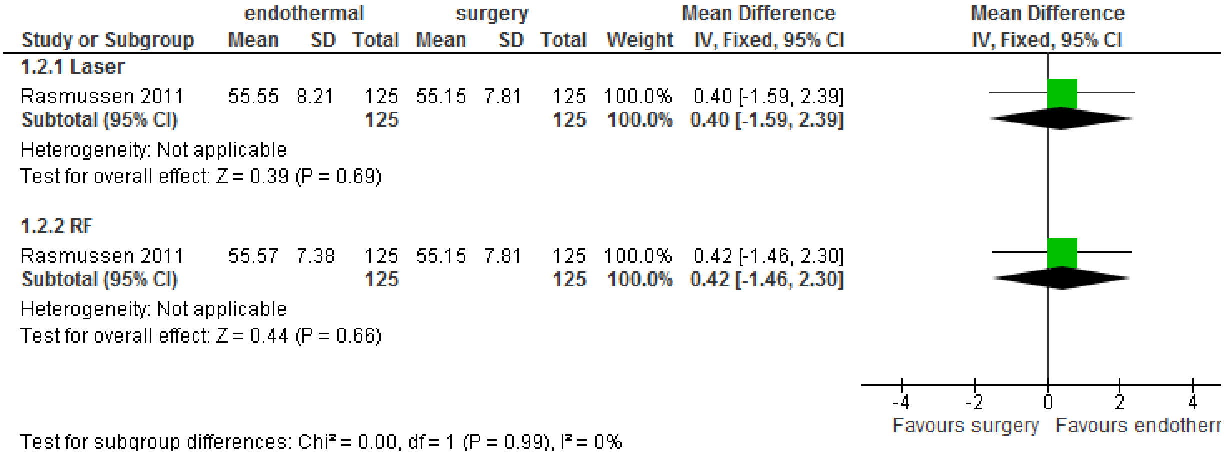
Figure 95: Stripping surgery vs. endothermal ablation in primary VV: SF-36 Physical 4 weeks



	endothermal			surgery				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 Laser									
Rasmussen 2011	47.68	6.95	125	48.13	7.21	125	100.0%	-0.45 [-2.21, 1.31]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-0.45 [-2.21, 1.31]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.50 (P = 0.62)									
1.1.2 RF									
Rasmussen 2011	49.88	7	125	48.13	7.21	125	100.0%	1.75 [-0.01, 3.51]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**1.75 [-0.01, 3.51]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.95 (P = 0.05)									

Test for subgroup differences: Chi² = 3.01, df = 1 (P = 0.08), I² = 66.7%

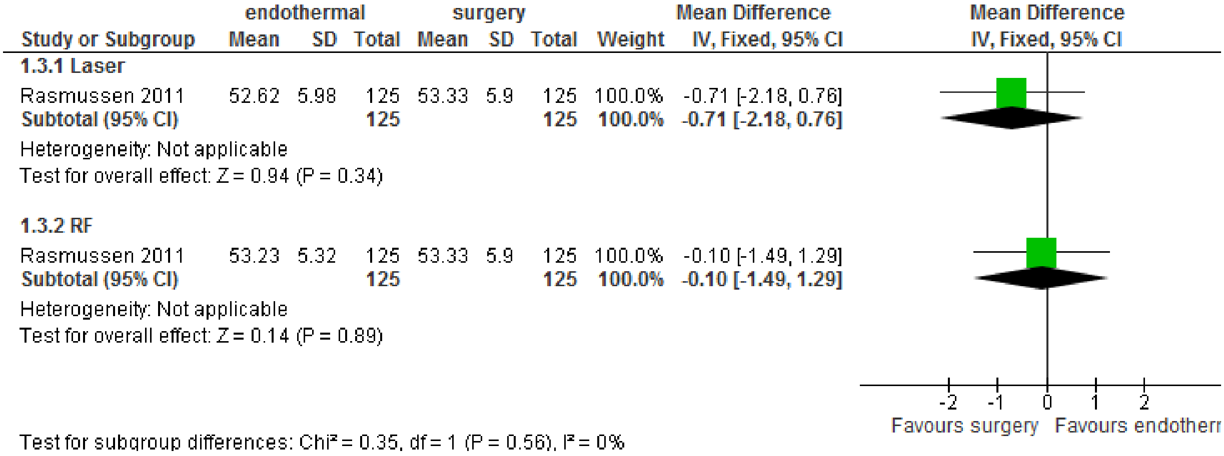
Figure 96: Stripping surgery vs. endothermal ablation in primary VV: SF-36 mental 4 weeks



	endothermal			surgery				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.1 Laser									
Rasmussen 2011	55.55	8.21	125	55.15	7.81	125	100.0%	0.40 [-1.59, 2.39]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.40 [-1.59, 2.39]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.39 (P = 0.69)									
1.2.2 RF									
Rasmussen 2011	55.57	7.38	125	55.15	7.81	125	100.0%	0.42 [-1.46, 2.30]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.42 [-1.46, 2.30]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.44 (P = 0.66)									

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%

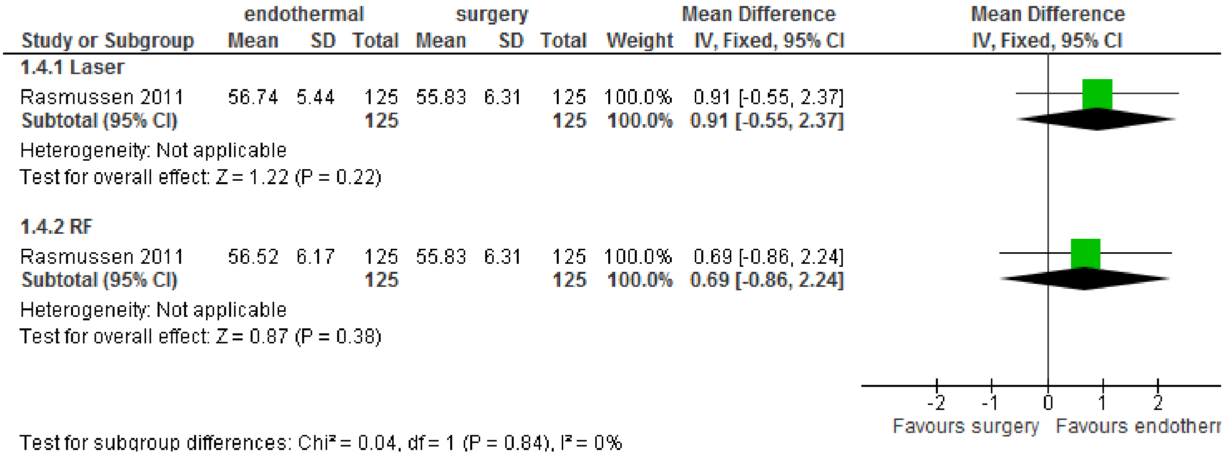
Figure 97: Stripping surgery vs. endothermal ablation in primary VV:SF-36 Physical 1 year



	endothermal			surgery				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 Laser									
Rasmussen 2011	52.62	5.98	125	53.33	5.9	125	100.0%	-0.71 [-2.18, 0.76]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-0.71 [-2.18, 0.76]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.94 (P = 0.34)									
1.3.2 RF									
Rasmussen 2011	53.23	5.32	125	53.33	5.9	125	100.0%	-0.10 [-1.49, 1.29]	
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-0.10 [-1.49, 1.29]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.14 (P = 0.89)									

Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%

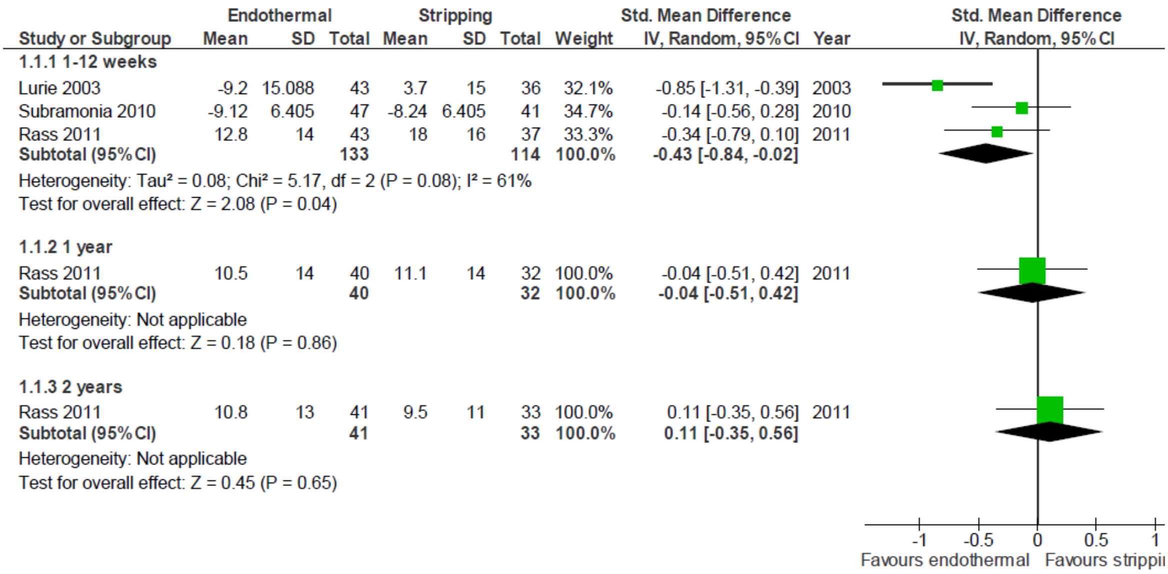
Figure 98: Stripping surgery vs. endothermal ablation in primary VV: SF-36 mental 1 year



	endothermal			surgery				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.4.1 Laser								
Rasmussen 2011	56.74	5.44	125	55.83	6.31	125	100.0%	0.91 [-0.55, 2.37]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.91 [-0.55, 2.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.22 (P = 0.22)								
1.4.2 RF								
Rasmussen 2011	56.52	6.17	125	55.83	6.31	125	100.0%	0.69 [-0.86, 2.24]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.69 [-0.86, 2.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.38)								

Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%

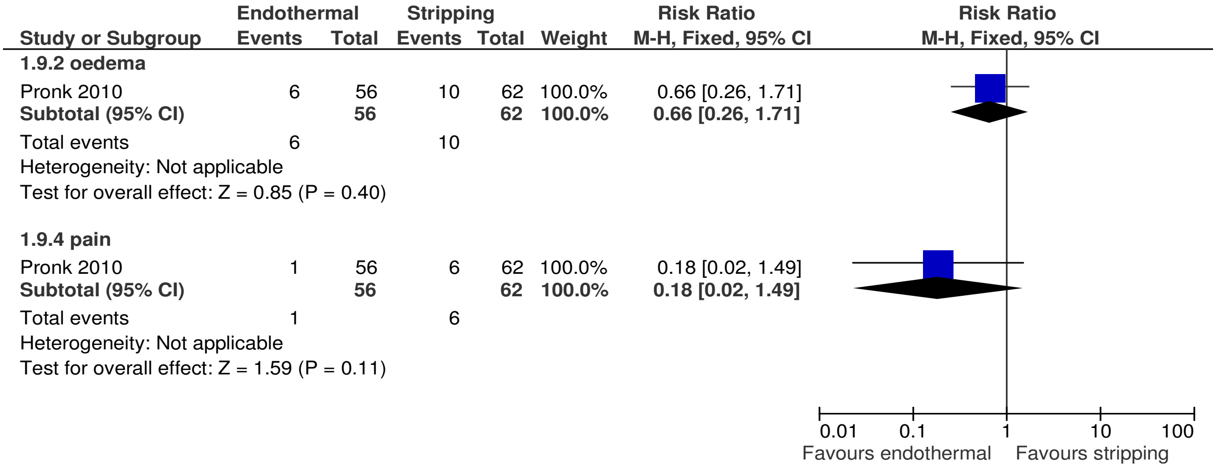
Figure 99: Stripping surgery vs. endothermal ablation in primary VV: Global quality of life – follow-up 1-12 weeks, 1 year and 2 years



	Endothermal			Stripping				Std. Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
1.1.1 1-12 weeks									
Lurie 2003	-9.2	15.088	43	3.7	15	36	32.1%	-0.85 [-1.31, -0.39]	2003
Subramonia 2010	-9.12	6.405	47	-8.24	6.405	41	34.7%	-0.14 [-0.56, 0.28]	2010
Rass 2011	12.8	14	43	18	16	37	33.3%	-0.34 [-0.79, 0.10]	2011
Subtotal (95% CI)			**133**			**114**	**100.0%**	**-0.43 [-0.84, -0.02]**	
Heterogeneity: Tau² = 0.08; Chi² = 5.17, df = 2 (P = 0.08); I² = 61%									
Test for overall effect: Z = 2.08 (P = 0.04)									
1.1.2 1 year									
Rass 2011	10.5	14	40	11.1	14	32	100.0%	-0.04 [-0.51, 0.42]	2011
Subtotal (95% CI)			**40**			**32**	**100.0%**	**-0.04 [-0.51, 0.42]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.18 (P = 0.86)									
1.1.3 2 years									
Rass 2011	10.8	13	41	9.5	11	33	100.0%	0.11 [-0.35, 0.56]	2011
Subtotal (95% CI)			**41**			**33**	**100.0%**	**0.11 [-0.35, 0.56]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.45 (P = 0.65)									

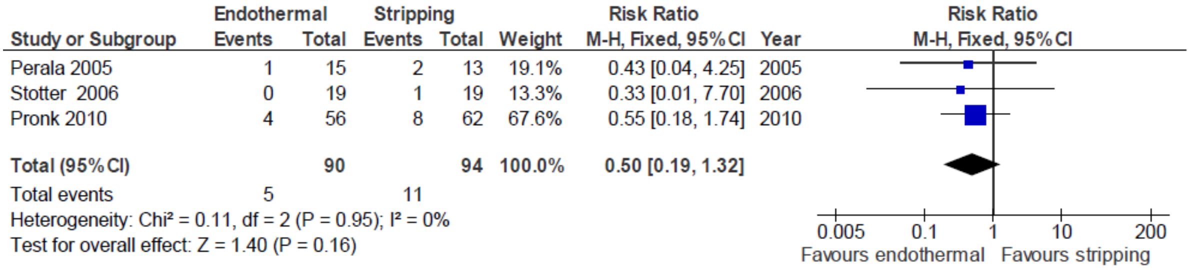
[Note that Subramonia 2010 used AVVQ, whilst Rass 2012 and Lurie 2003 used CIVIQ -2 – hence the use of standardised mean differences]

Figure 100: Stripping surgery vs. endothermal ablation in primary VV: Patient reported symptoms – oedema and pain (dichotomous)



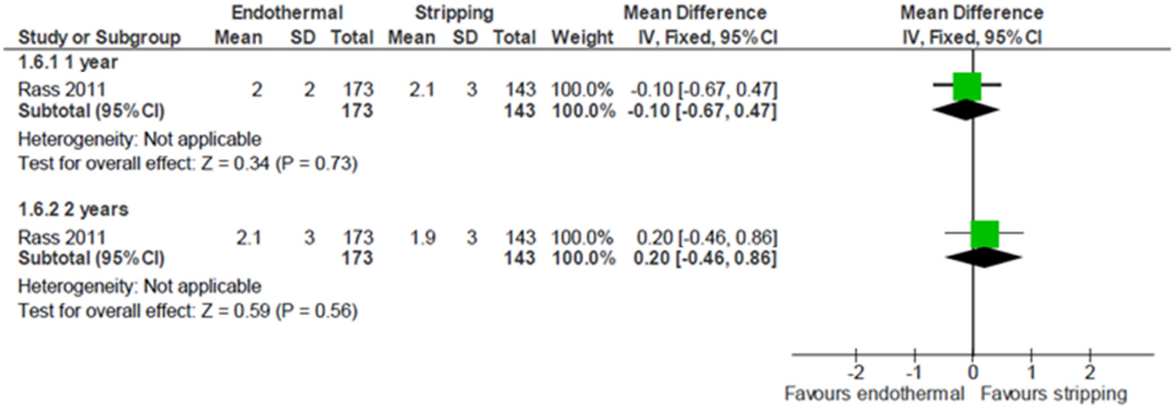
Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.2 oedema						
Pronk 2010	6	56	10	62	100.0%	0.66 [0.26, 1.71]
Subtotal (95% CI)		**56**		**62**	**100.0%**	**0.66 [0.26, 1.71]**
Total events	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
1.9.4 pain						
Pronk 2010	1	56	6	62	100.0%	0.18 [0.02, 1.49]
Subtotal (95% CI)		**56**		**62**	**100.0%**	**0.18 [0.02, 1.49]**
Total events	1		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						

Figure 101: Stripping surgery vs. endothermal ablation in primary VV: dissatisfaction with body image



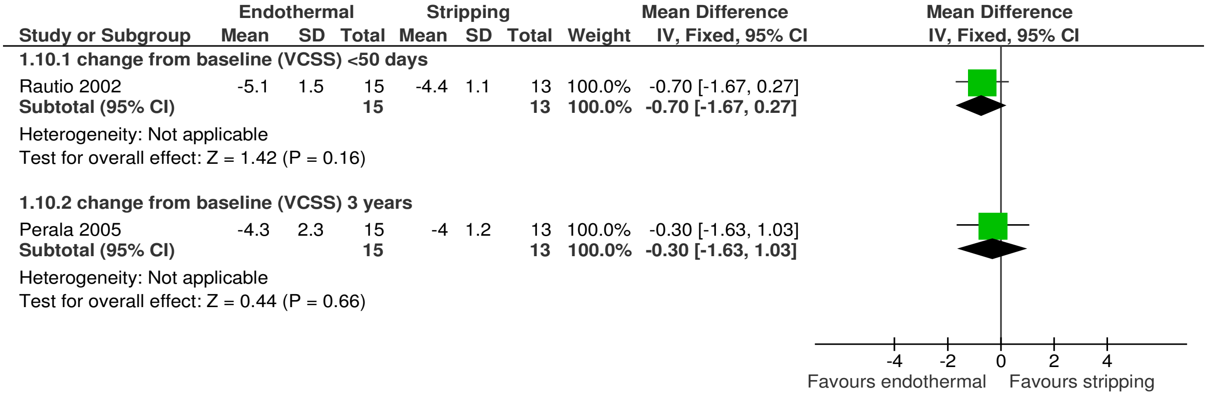
Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Perala 2005	1	15	2	13	19.1%	0.43 [0.04, 4.25]	2005
Stotter 2006	0	19	1	19	13.3%	0.33 [0.01, 7.70]	2006
Pronk 2010	4	56	8	62	67.6%	0.55 [0.18, 1.74]	2010
Total (95% CI)		**90**		**94**	**100.0%**	**0.50 [0.19, 1.32]**	
Total events	5		11				
Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%							
Test for overall effect: Z = 1.40 (P = 0.16)							

Figure 102: Stripping surgery vs. endothermal ablation in primary VV: Physician reported disease severity (post-test; continuous)



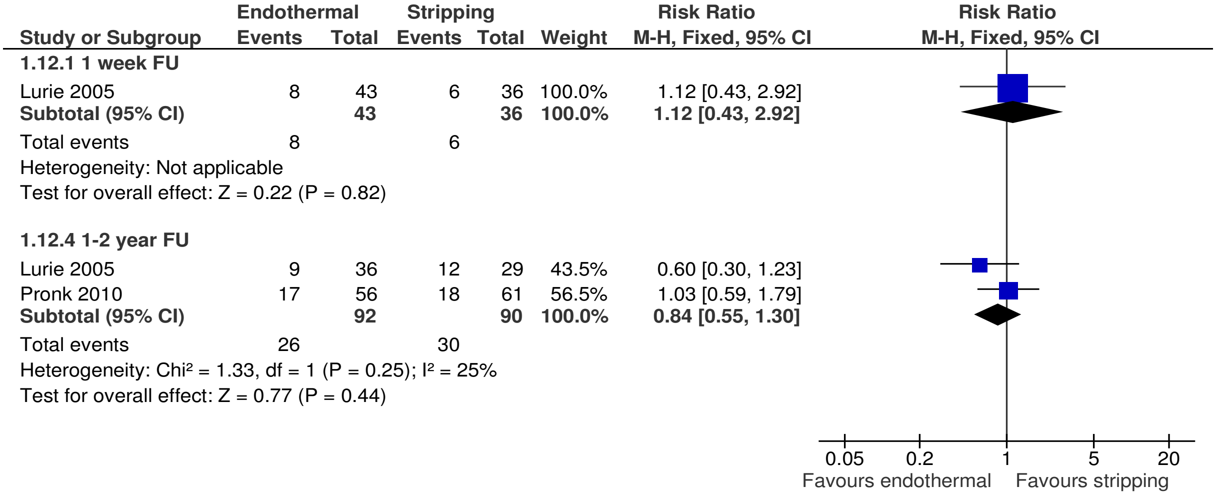
Study or Subgroup	Endothermal Mean	Endothermal SD	Endothermal Total	Stripping Mean	Stripping SD	Stripping Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 1 year								
Rass 2011	2	2	173	2.1	3	143	100.0%	-0.10 [-0.67, 0.47]
Subtotal (95% CI)			**173**			**143**	**100.0%**	**-0.10 [-0.67, 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
1.6.2 2 years								
Rass 2011	2.1	3	173	1.9	3	143	100.0%	0.20 [-0.46, 0.86]
Subtotal (95% CI)			**173**			**143**	**100.0%**	**0.20 [-0.46, 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.56)								

Figure 103: Stripping surgery vs. endothermal ablation in primary VV: Physician reported disease severity (change from baseline; continuous)



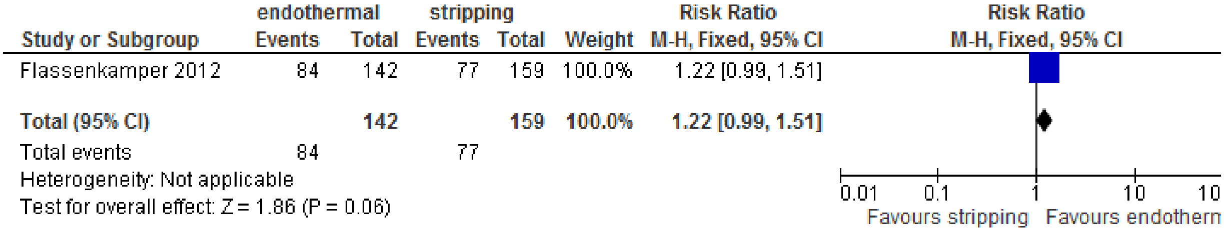
Study or Subgroup	Endothermal Mean	Endothermal SD	Endothermal Total	Stripping Mean	Stripping SD	Stripping Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 change from baseline (VCSS) <50 days								
Rautio 2002	-5.1	1.5	15	-4.4	1.1	13	100.0%	-0.70 [-1.67, 0.27]
Subtotal (95% CI)			**15**			**13**	**100.0%**	**-0.70 [-1.67, 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.42 (P = 0.16)								
1.10.2 change from baseline (VCSS) 3 years								
Perala 2005	-4.3	2.3	15	-4	1.2	13	100.0%	-0.30 [-1.63, 1.03]
Subtotal (95% CI)			**15**			**13**	**100.0%**	**-0.30 [-1.63, 1.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.44 (P = 0.66)								

Figure 104: stripping surgery vs. endothermal ablation in primary VV: Physician reported disease severity (dichotomous)



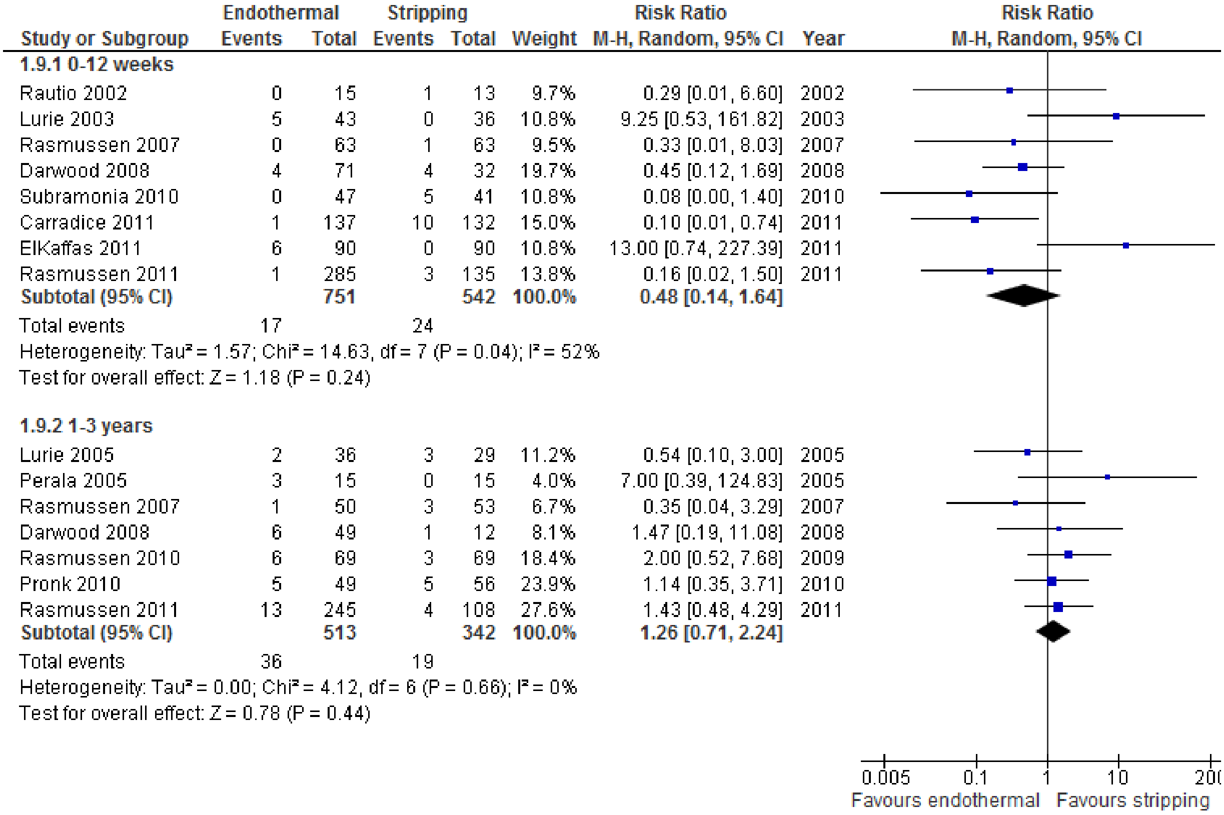
Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 1 week FU						
Lurie 2005	8	43	6	36	100.0%	1.12 [0.43, 2.92]
Subtotal (95% CI)		**43**		**36**	**100.0%**	**1.12 [0.43, 2.92]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.12.4 1-2 year FU						
Lurie 2005	9	36	12	29	43.5%	0.60 [0.30, 1.23]
Pronk 2010	17	56	18	61	56.5%	1.03 [0.59, 1.79]
Subtotal (95% CI)		**92**		**90**	**100.0%**	**0.84 [0.55, 1.30]**
Total events	26		30			
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%						
Test for overall effect: Z = 0.77 (P = 0.44)						

Figure 105: Stripping surgery vs. endothermal ablation in primary VV: Physician reported disease severity (dichotomous) – asymptomatic according to VDS



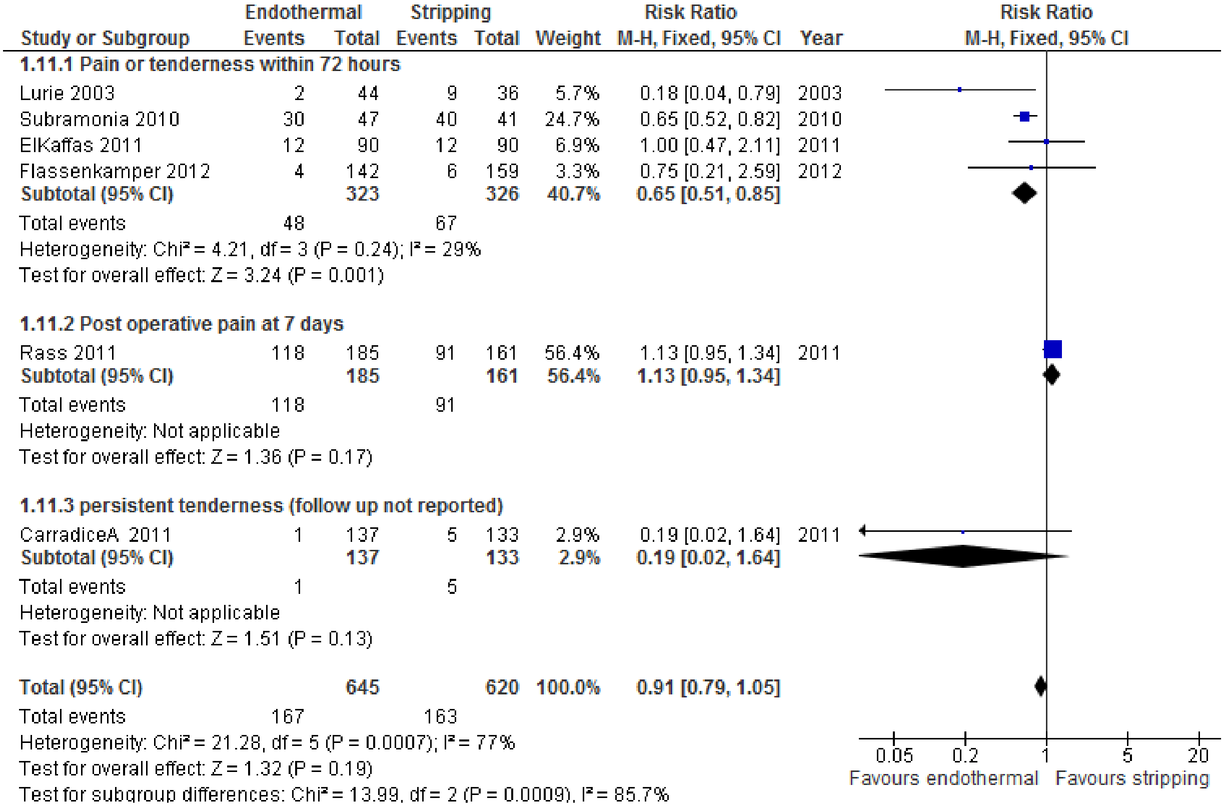
Study or Subgroup	endothermal Events	endothermal Total	stripping Events	stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Flassenkamper 2012	84	142	77	159	100.0%	1.22 [0.99, 1.51]
Total (95% CI)		**142**		**159**	**100.0%**	**1.22 [0.99, 1.51]**
Total events	84		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						

Figure 106: Stripping surgery vs. endothermal ablation in primary VV: GSV reflux



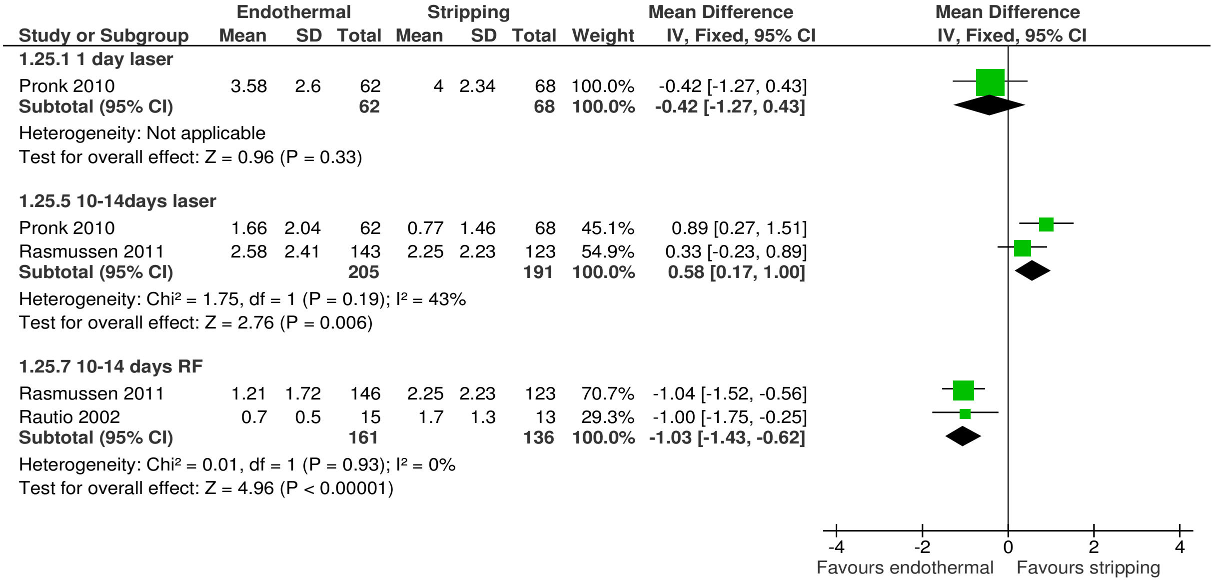
	Endothermal		Stripping			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
1.9.1 0-12 weeks							
Rautio 2002	0	15	1	13	9.7%	0.29 [0.01, 6.60]	2002
Lurie 2003	5	43	0	36	10.8%	9.25 [0.53, 161.82]	2003
Rasmussen 2007	0	63	1	63	9.5%	0.33 [0.01, 8.03]	2007
Darwood 2008	4	71	4	32	19.7%	0.45 [0.12, 1.69]	2008
Subramonia 2010	0	47	5	41	10.8%	0.08 [0.00, 1.40]	2010
Carradice 2011	1	137	10	132	15.0%	0.10 [0.01, 0.74]	2011
ElKaffas 2011	6	90	0	90	10.8%	13.00 [0.74, 227.39]	2011
Rasmussen 2011	1	285	3	135	13.8%	0.16 [0.02, 1.50]	2011
Subtotal (95% CI)		**751**		**542**	**100.0%**	**0.48 [0.14, 1.64]**	
Total events	17		24				
Heterogeneity: Tau^2 = 1.57; Chi^2 = 14.63, df = 7 (P = 0.04); I^2 = 52%							
Test for overall effect: Z = 1.18 (P = 0.24)							
1.9.2 1-3 years							
Lurie 2005	2	36	3	29	11.2%	0.54 [0.10, 3.00]	2005
Perala 2005	3	15	0	15	4.0%	7.00 [0.39, 124.83]	2005
Rasmussen 2007	1	50	3	53	6.7%	0.35 [0.04, 3.29]	2007
Darwood 2008	6	49	1	12	8.1%	1.47 [0.19, 11.08]	2008
Rasmussen 2010	6	69	3	69	18.4%	2.00 [0.52, 7.68]	2009
Pronk 2010	5	49	5	56	23.9%	1.14 [0.35, 3.71]	2010
Rasmussen 2011	13	245	4	108	27.6%	1.43 [0.48, 4.29]	2011
Subtotal (95% CI)		**513**		**342**	**100.0%**	**1.26 [0.71, 2.24]**	
Total events	36		19				
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.12, df = 6 (P = 0.66); I^2 = 0%							
Test for overall effect: Z = 0.78 (P = 0.44)							

Figure 107: Stripping surgery vs. endothermal ablation in primary VV: Adverse events – post op pain (dichotomous



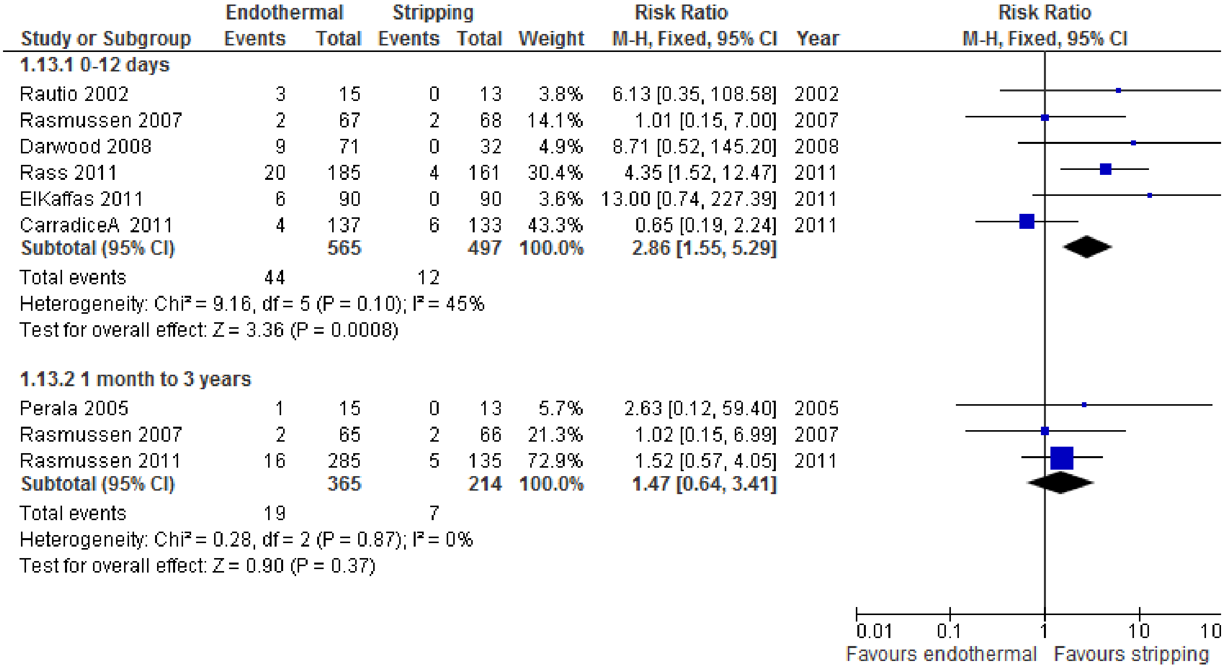
	Endothermal		Stripping			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
1.11.1 Pain or tenderness within 72 hours							
Lurie 2003	2	44	9	36	5.7%	0.18 [0.04, 0.79]	2003
Subramonia 2010	30	47	40	41	24.7%	0.65 [0.52, 0.82]	2010
ElKaffas 2011	12	90	12	90	6.9%	1.00 [0.47, 2.11]	2011
Flassenkamper 2012	4	142	6	159	3.3%	0.75 [0.21, 2.59]	2012
Subtotal (95% CI)		**323**		**326**	**40.7%**	**0.65 [0.51, 0.85]**	
Total events	48		67				
Heterogeneity: Chi² = 4.21, df = 3 (P = 0.24); I² = 29%							
Test for overall effect: Z = 3.24 (P = 0.001)							
1.11.2 Post operative pain at 7 days							
Rass 2011	118	185	91	161	56.4%	1.13 [0.95, 1.34]	2011
Subtotal (95% CI)		**185**		**161**	**56.4%**	**1.13 [0.95, 1.34]**	
Total events	118		91				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.36 (P = 0.17)							
1.11.3 persistent tenderness (follow up not reported)							
CarradiceA 2011	1	137	5	133	2.9%	0.19 [0.02, 1.64]	2011
Subtotal (95% CI)		**137**		**133**	**2.9%**	**0.19 [0.02, 1.64]**	
Total events	1		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.51 (P = 0.13)							
Total (95% CI)		**645**		**620**	**100.0%**	**0.91 [0.79, 1.05]**	
Total events	167		163				
Heterogeneity: Chi² = 21.28, df = 5 (P = 0.0007); I² = 77%							
Test for overall effect: Z = 1.32 (P = 0.19)							
Test for subgroup differences: Chi² = 13.99, df = 2 (P = 0.0009), I² = 85.7%							

Figure 108: Stripping surgery vs. endothermal ablation in primary VV: Adverse events - Post op pain (continuous variable)



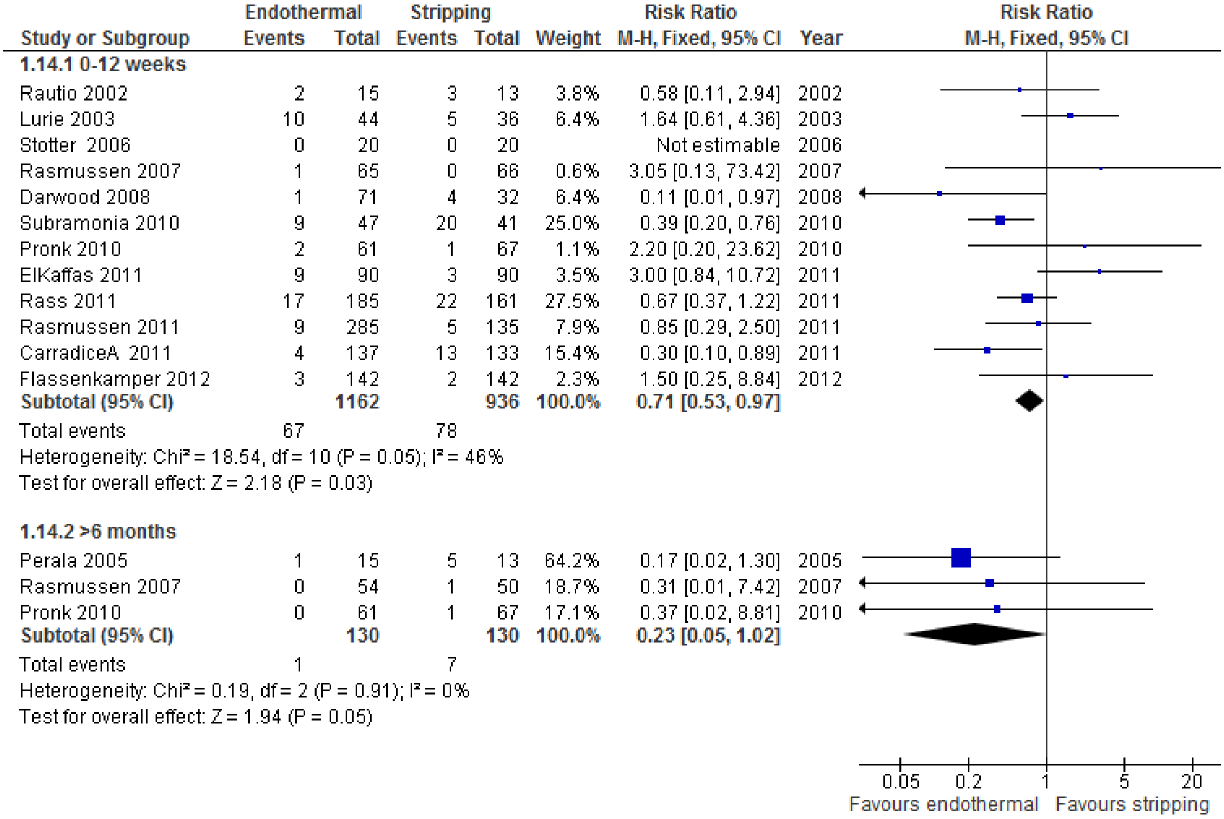
	Endothermal			Stripping				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
1.25.1 1 day laser								
Pronk 2010	3.58	2.6	62	4	2.34	68	100.0%	-0.42 [-1.27, 0.43]
Subtotal (95% CI)			**62**			**68**	**100.0%**	**-0.42 [-1.27, 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.96 (P = 0.33)								
1.25.5 10-14days laser								
Pronk 2010	1.66	2.04	62	0.77	1.46	68	45.1%	0.89 [0.27, 1.51]
Rasmussen 2011	2.58	2.41	143	2.25	2.23	123	54.9%	0.33 [-0.23, 0.89]
Subtotal (95% CI)			**205**			**191**	**100.0%**	**0.58 [0.17, 1.00]**
Heterogeneity: Chi² = 1.75, df = 1 (P = 0.19); I² = 43%								
Test for overall effect: Z = 2.76 (P = 0.006)								
1.25.7 10-14 days RF								
Rasmussen 2011	1.21	1.72	146	2.25	2.23	123	70.7%	-1.04 [-1.52, -0.56]
Rautio 2002	0.7	0.5	15	1.7	1.3	13	29.3%	-1.00 [-1.75, -0.25]
Subtotal (95% CI)			**161**			**136**	**100.0%**	**-1.03 [-1.43, -0.62]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 4.96 (P < 0.00001)								

Figure 109: Stripping surgery vs. endothermal ablation in primary VV: Adverse events – phlebitis/thrombophlebitis



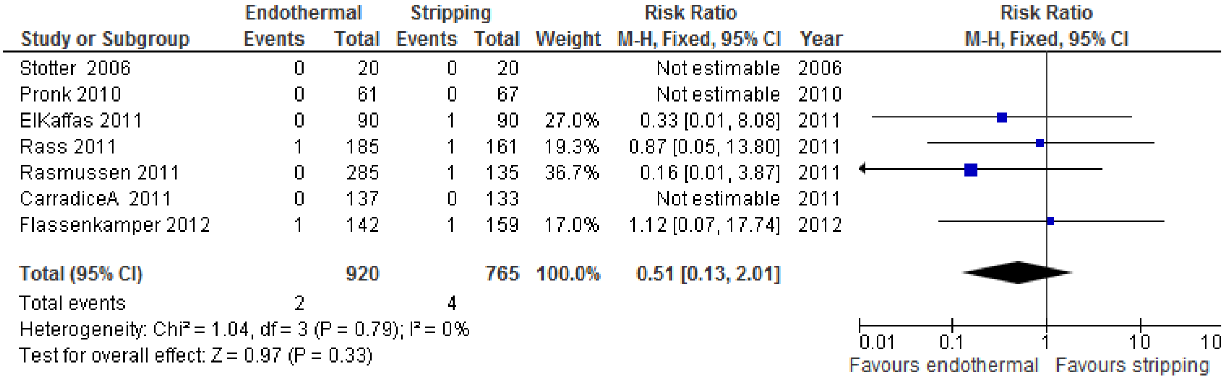
Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.13.1 0-12 days							
Rautio 2002	3	15	0	13	3.8%	6.13 [0.35, 108.58]	2002
Rasmussen 2007	2	67	2	68	14.1%	1.01 [0.15, 7.00]	2007
Darwood 2008	9	71	0	32	4.9%	8.71 [0.52, 145.20]	2008
Rass 2011	20	185	4	161	30.4%	4.35 [1.52, 12.47]	2011
ElKaffas 2011	6	90	0	90	3.6%	13.00 [0.74, 227.39]	2011
CarradiceA 2011	4	137	6	133	43.3%	0.65 [0.19, 2.24]	2011
Subtotal (95% CI)		**565**		**497**	**100.0%**	**2.86 [1.55, 5.29]**	
Total events	44		12				
Heterogeneity: Chi² = 9.16, df = 5 (P = 0.10); I² = 45%							
Test for overall effect: Z = 3.36 (P = 0.0008)							
1.13.2 1 month to 3 years							
Perala 2005	1	15	0	13	5.7%	2.63 [0.12, 59.40]	2005
Rasmussen 2007	2	65	2	66	21.3%	1.02 [0.15, 6.99]	2007
Rasmussen 2011	16	285	5	135	72.9%	1.52 [0.57, 4.05]	2011
Subtotal (95% CI)		**365**		**214**	**100.0%**	**1.47 [0.64, 3.41]**	
Total events	19		7				
Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.90 (P = 0.37)							

Figure 110: Stripping surgery vs. endothermal ablation in primary VV: Adverse events – sensory deficits/neural injury



Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.14.1 0-12 weeks							
Rautio 2002	2	15	3	13	3.8%	0.58 [0.11, 2.94]	2002
Lurie 2003	10	44	5	36	6.4%	1.64 [0.61, 4.36]	2003
Stotter 2006	0	20	0	20		Not estimable	2006
Rasmussen 2007	1	65	0	66	0.6%	3.05 [0.13, 73.42]	2007
Darwood 2008	1	71	4	32	6.4%	0.11 [0.01, 0.97]	2008
Subramonia 2010	9	47	20	41	25.0%	0.39 [0.20, 0.76]	2010
Pronk 2010	2	61	1	67	1.1%	2.20 [0.20, 23.62]	2010
ElKaffas 2011	9	90	3	90	3.5%	3.00 [0.84, 10.72]	2011
Rass 2011	17	185	22	161	27.5%	0.67 [0.37, 1.22]	2011
Rasmussen 2011	9	285	5	135	7.9%	0.85 [0.29, 2.50]	2011
CarradiceA 2011	4	137	13	133	15.4%	0.30 [0.10, 0.89]	2011
Flassenkamper 2012	3	142	2	142	2.3%	1.50 [0.25, 8.84]	2012
Subtotal (95% CI)		**1162**		**936**	**100.0%**	**0.71 [0.53, 0.97]**	
Total events	67		78				
Heterogeneity: Chi² = 18.54, df = 10 (P = 0.05); I² = 46%							
Test for overall effect: Z = 2.18 (P = 0.03)							
1.14.2 >6 months							
Perala 2005	1	15	5	13	64.2%	0.17 [0.02, 1.30]	2005
Rasmussen 2007	0	54	1	50	18.7%	0.31 [0.01, 7.42]	2007
Pronk 2010	0	61	1	67	17.1%	0.37 [0.02, 8.81]	2010
Subtotal (95% CI)		**130**		**130**	**100.0%**	**0.23 [0.05, 1.02]**	
Total events	1		7				
Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.94 (P = 0.05)							

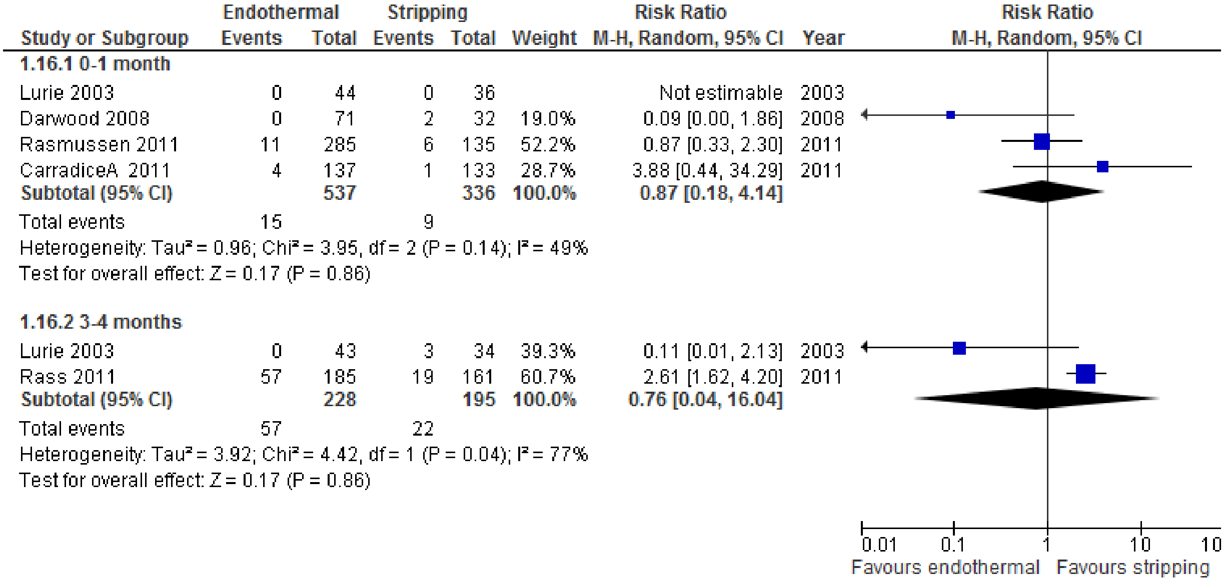
Figure 111: Stripping surgery vs. endothermal ablation in primary VV: Adverse events - DVT



Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Stotter 2006	0	20	0	20		Not estimable	2006
Pronk 2010	0	61	0	67		Not estimable	2010
ElKaffas 2011	0	90	1	90	27.0%	0.33 [0.01, 8.08]	2011
Rass 2011	1	185	1	161	19.3%	0.87 [0.05, 13.80]	2011
Rasmussen 2011	0	285	1	135	36.7%	0.16 [0.01, 3.87]	2011
CarradiceA 2011	0	137	0	133		Not estimable	2011
Flassenkamper 2012	1	142	1	159	17.0%	1.12 [0.07, 17.74]	2012
Total (95% CI)		**920**		**765**	**100.0%**	**0.51 [0.13, 2.01]**	
Total events	2		4				

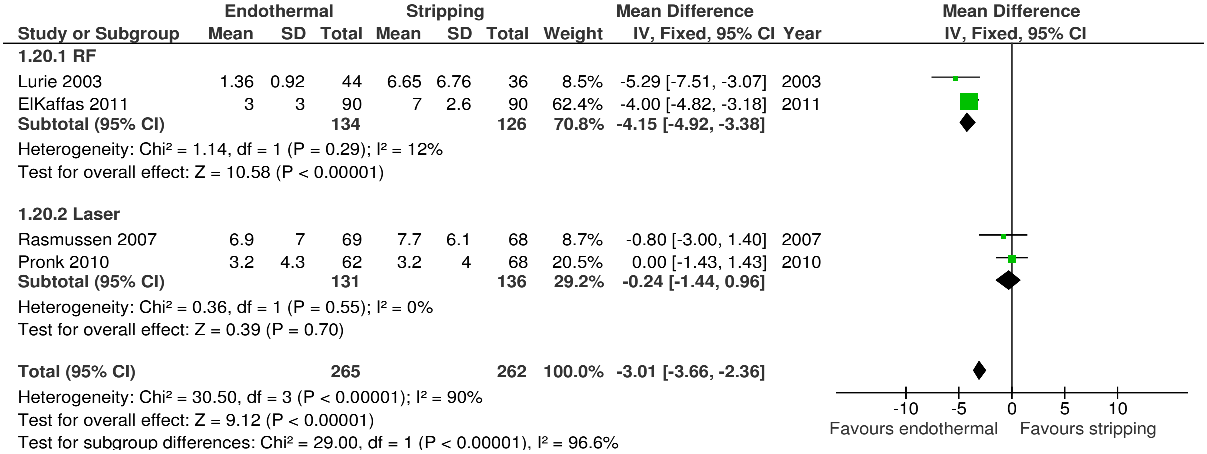
Heterogeneity: Chi² = 1.04, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

Figure 112: Stripping surgery vs. endothermal ablation in primary VV: Adverse events – limb discolouration



Study or Subgroup	Endothermal Events	Endothermal Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.16.1 0-1 month							
Lurie 2003	0	44	0	36		Not estimable	2003
Darwood 2008	0	71	2	32	19.0%	0.09 [0.00, 1.86]	2008
Rasmussen 2011	11	285	6	135	52.2%	0.87 [0.33, 2.30]	2011
CarradiceA 2011	4	137	1	133	28.7%	3.88 [0.44, 34.29]	2011
Subtotal (95% CI)		**537**		**336**	**100.0%**	**0.87 [0.18, 4.14]**	
Total events	15		9				
Heterogeneity: Tau² = 0.96; Chi² = 3.95, df = 2 (P = 0.14); I² = 49%							
Test for overall effect: Z = 0.17 (P = 0.86)							
1.16.2 3-4 months							
Lurie 2003	0	43	3	34	39.3%	0.11 [0.01, 2.13]	2003
Rass 2011	57	185	19	161	60.7%	2.61 [1.62, 4.20]	2011
Subtotal (95% CI)		**228**		**195**	**100.0%**	**0.76 [0.04, 16.04]**	
Total events	57		22				
Heterogeneity: Tau² = 3.92; Chi² = 4.42, df = 1 (P = 0.04); I² = 77%							
Test for overall effect: Z = 0.17 (P = 0.86)							

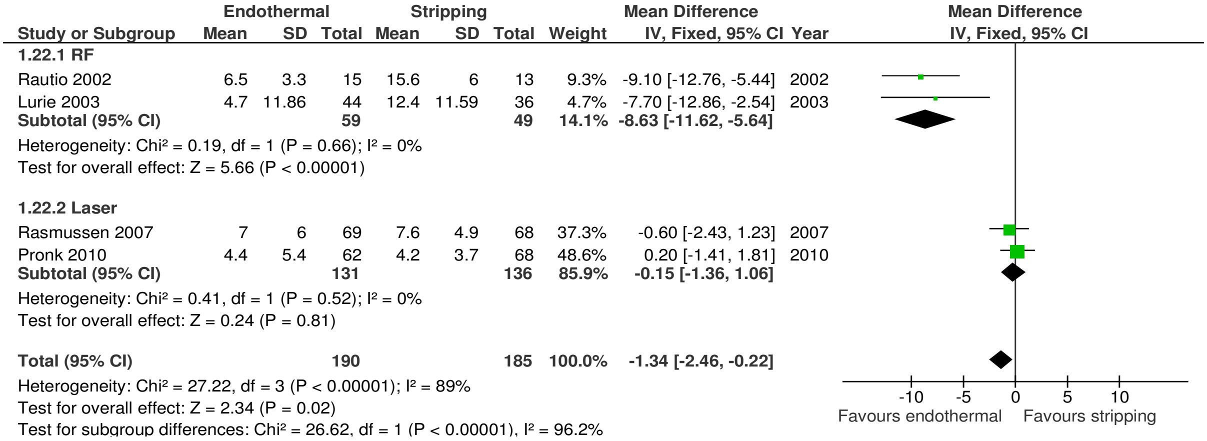
Figure 113: Stripping surgery vs. endothermal ablation in primary VV: Return to normal activities by endothermal type



Study or Subgroup	Endothermal Mean	Endothermal SD	Endothermal Total	Stripping Mean	Stripping SD	Stripping Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.20.1 RF									
Lurie 2003	1.36	0.92	44	6.65	6.76	36	8.5%	-5.29 [-7.51, -3.07]	2003
ElKaffas 2011	3	3	90	7	2.6	90	62.4%	-4.00 [-4.82, -3.18]	2011
Subtotal (95% CI)			**134**			**126**	**70.8%**	**-4.15 [-4.92, -3.38]**	
Heterogeneity: Chi² = 1.14, df = 1 (P = 0.29); I² = 12%									
Test for overall effect: Z = 10.58 (P < 0.00001)									
1.20.2 Laser									
Rasmussen 2007	6.9	7	69	7.7	6.1	68	8.7%	-0.80 [-3.00, 1.40]	2007
Pronk 2010	3.2	4.3	62	3.2	4	68	20.5%	0.00 [-1.43, 1.43]	2010
Subtotal (95% CI)			**131**			**136**	**29.2%**	**-0.24 [-1.44, 0.96]**	
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%									
Test for overall effect: Z = 0.39 (P = 0.70)									
Total (95% CI)			**265**			**262**	**100.0%**	**-3.01 [-3.66, -2.36]**	

Heterogeneity: Chi² = 30.50, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 9.12 (P < 0.00001)
Test for subgroup differences: Chi² = 29.00, df = 1 (P < 0.00001), I² = 96.6%

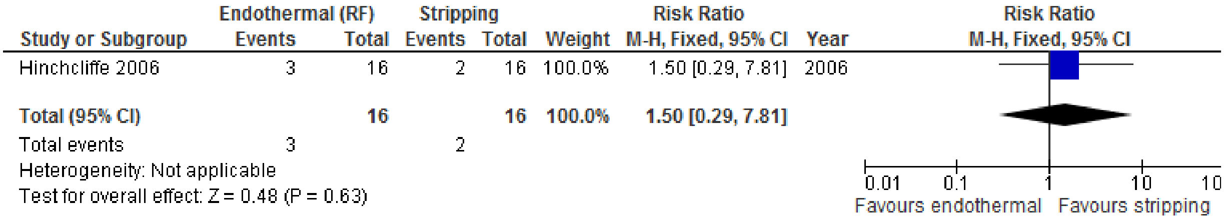
Figure 114: Stripping surgery vs. endothermal ablation in primary VV: Return to work by endothermal type



Study or Subgroup	Endothermal			Stripping				Mean Difference	Year
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	
1.22.1 RF									
Rautio 2002	6.5	3.3	15	15.6	6	13	9.3%	-9.10 [-12.76, -5.44]	2002
Lurie 2003	4.7	11.86	44	12.4	11.59	36	4.7%	-7.70 [-12.86, -2.54]	2003
Subtotal (95% CI)			**59**			**49**	**14.1%**	**-8.63 [-11.62, -5.64]**	
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%									
Test for overall effect: Z = 5.66 (P < 0.00001)									
1.22.2 Laser									
Rasmussen 2007	7	6	69	7.6	4.9	68	37.3%	-0.60 [-2.43, 1.23]	2007
Pronk 2010	4.4	5.4	62	4.2	3.7	68	48.6%	0.20 [-1.41, 1.81]	2010
Subtotal (95% CI)			**131**			**136**	**85.9%**	**-0.15 [-1.36, 1.06]**	
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%									
Test for overall effect: Z = 0.24 (P = 0.81)									
Total (95% CI)			**190**			**185**	**100.0%**	**-1.34 [-2.46, -0.22]**	
Heterogeneity: Chi² = 27.22, df = 3 (P < 0.00001); I² = 89%									
Test for overall effect: Z = 2.34 (P = 0.02)									
Test for subgroup differences: Chi² = 26.62, df = 1 (P < 0.00001), I² = 96.2%									

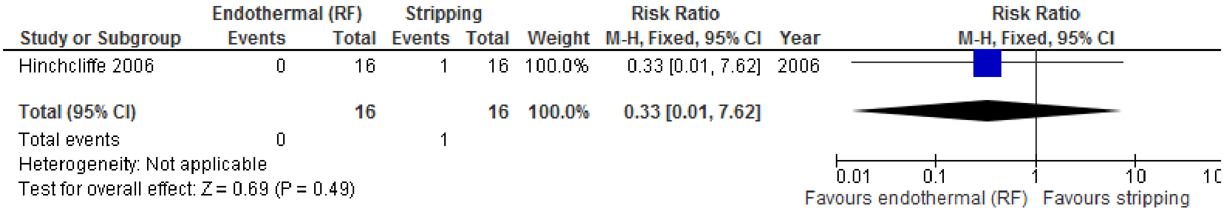
I.3.2.2 Recurrent varicose veins

Figure 115: Stripping surgery vs. endothermal ablation in recurrent VV: GSV reflux – 6 weeks



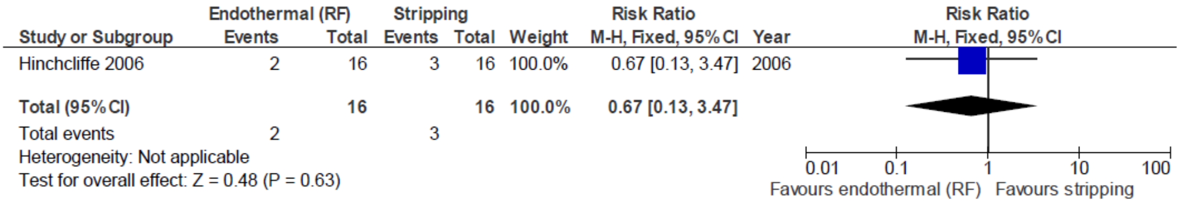
Study or Subgroup	Endothermal (RF)		Stripping			Risk Ratio	Year
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Hinchcliffe 2006	3	16	2	16	100.0%	1.50 [0.29, 7.81]	2006
Total (95% CI)		**16**		**16**	**100.0%**	**1.50 [0.29, 7.81]**	
Total events	3		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							

Figure 116: Stripping surgery vs. endothermal ablation in recurrent VV:Adverse events – thrombophlebitis (6 weeks)



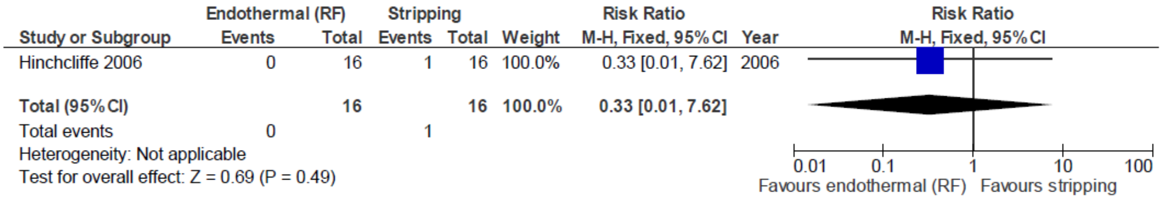
Study or Subgroup	Endothermal (RF)		Stripping			Risk Ratio	Year
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Hinchcliffe 2006	0	16	1	16	100.0%	0.33 [0.01, 7.62]	2006
Total (95% CI)		**16**		**16**	**100.0%**	**0.33 [0.01, 7.62]**	
Total events	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							

Figure 117: Stripping surgery vs. endothermal ablation in recurrent VV:Adverse events – sensory deficits / neural injury (neuralgia and numbness at 6 weeks)



Study or Subgroup	Endothermal (RF)		Stripping			Risk Ratio	Year
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Hinchcliffe 2006	2	16	3	16	100.0%	0.67 [0.13, 3.47]	2006
Total (95% CI)		**16**		**16**	**100.0%**	**0.67 [0.13, 3.47]**	
Total events	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							

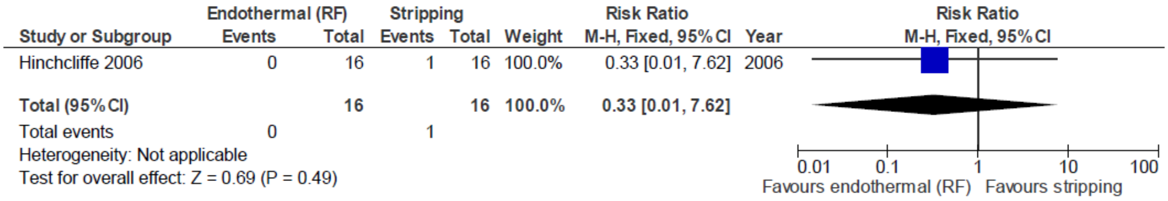
Figure 118: Stripping surgery vs. endothermal ablation in recurrent VV: Adverse events – infection (6 weeks)



Study or Subgroup	Endothermal (RF) Events	Endothermal (RF) Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hinchcliffe 2006	0	16	1	16	100.0%	0.33 [0.01, 7.62]	2006
Total (95% CI)		**16**		**16**	**100.0%**	**0.33 [0.01, 7.62]**	
Total events	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

Figure 119: Stripping surgery vs. endothermal ablation in recurrent VV: Adverse events - oedema

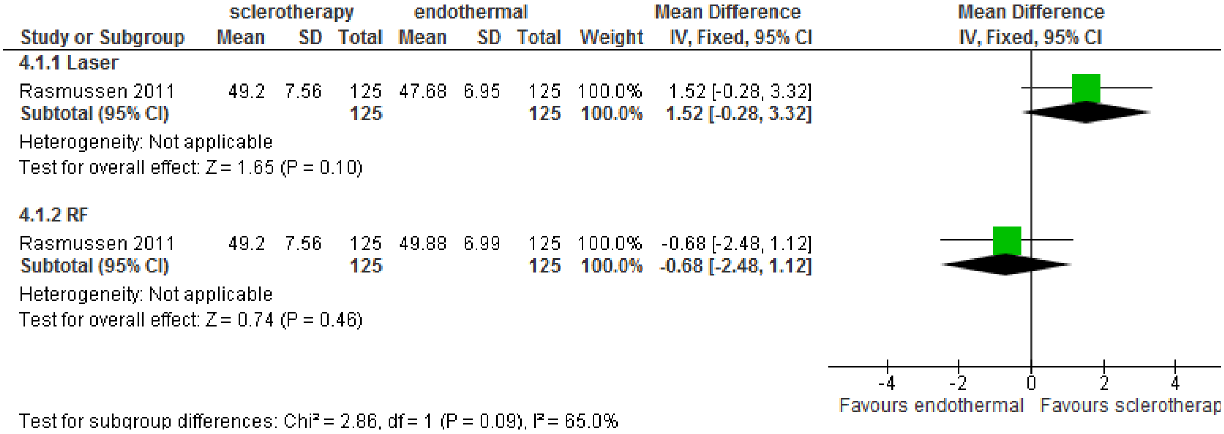


Study or Subgroup	Endothermal (RF) Events	Endothermal (RF) Total	Stripping Events	Stripping Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hinchcliffe 2006	0	16	1	16	100.0%	0.33 [0.01, 7.62]	2006
Total (95% CI)		**16**		**16**	**100.0%**	**0.33 [0.01, 7.62]**	
Total events	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

I.3.3 Foam sclerotherapy vs. endothermal ablation

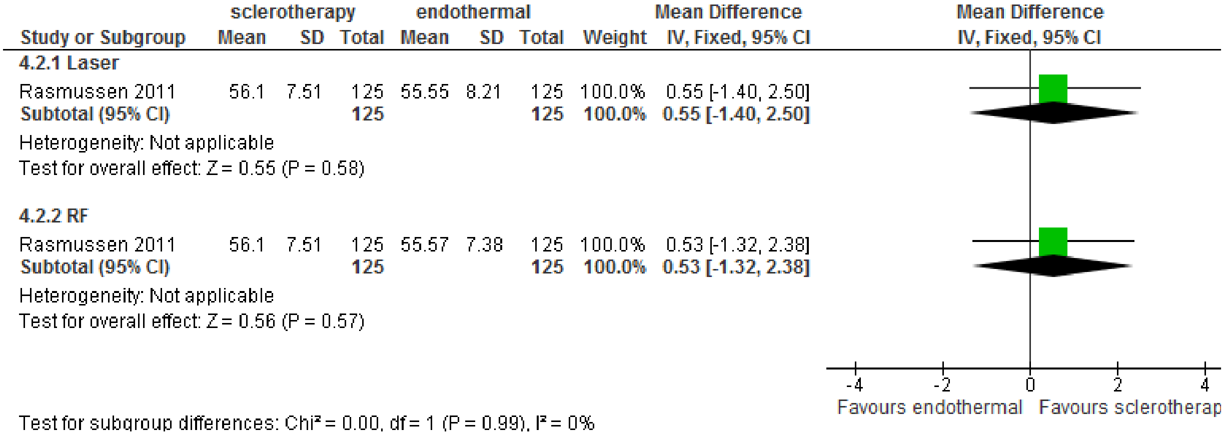
Figure 120: Foam sclerotherapy vs. endothermal ablation: SF-36 Physical 4 weeks



Study or Subgroup	sclerotherapy Mean	sclerotherapy SD	sclerotherapy Total	endothermal Mean	endothermal SD	endothermal Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 Laser								
Rasmussen 2011	49.2	7.56	125	47.68	6.95	125	100.0%	1.52 [-0.28, 3.32]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**1.52 [-0.28, 3.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
4.1.2 RF								
Rasmussen 2011	49.2	7.56	125	49.88	6.99	125	100.0%	-0.68 [-2.48, 1.12]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-0.68 [-2.48, 1.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								

Test for subgroup differences: Chi^2 = 2.86, df = 1 (P = 0.09), I^2 = 65.0%

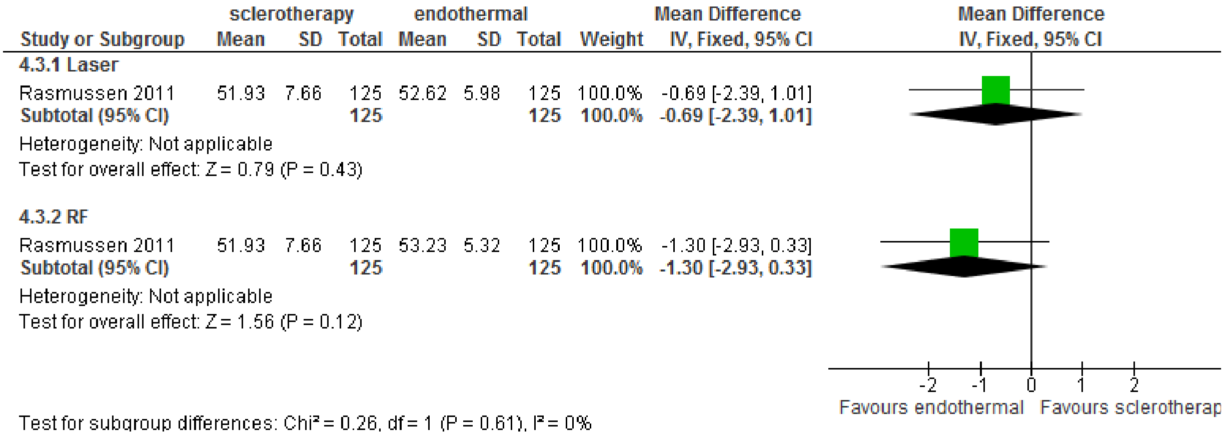
Figure 121: Foam sclerotherapy vs. endothermal ablation: SF-36 mental 4 weeks



Study or Subgroup	sclerotherapy Mean	sclerotherapy SD	sclerotherapy Total	endothermal Mean	endothermal SD	endothermal Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 Laser								
Rasmussen 2011	56.1	7.51	125	55.55	8.21	125	100.0%	0.55 [-1.40, 2.50]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.55 [-1.40, 2.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
4.2.2 RF								
Rasmussen 2011	56.1	7.51	125	55.57	7.38	125	100.0%	0.53 [-1.32, 2.38]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**0.53 [-1.32, 2.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.57)								

Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 = 0%

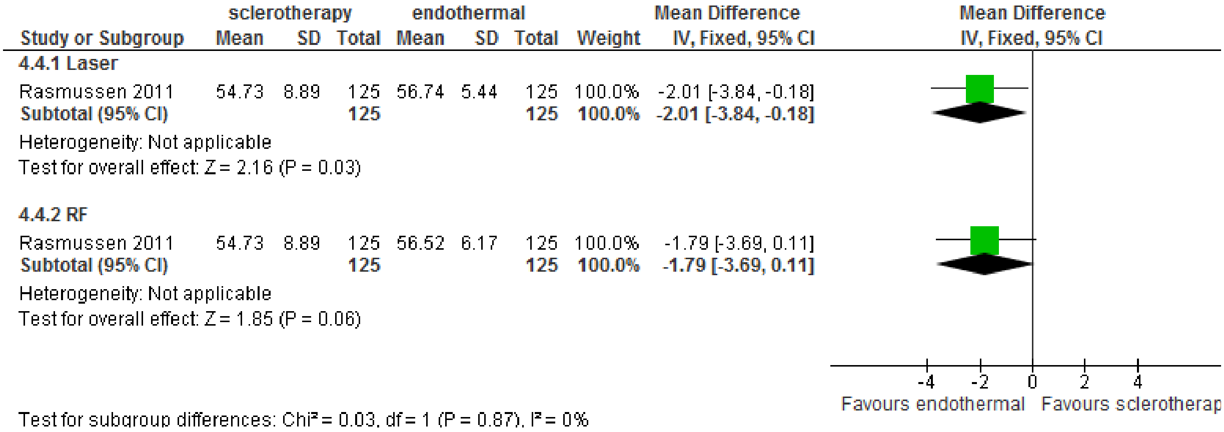
Figure 122: Foam sclerotherapy vs. endothermal ablation: SF-36 Physical 1 year



	sclerotherapy			endothermal				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
4.3.1 Laser								
Rasmussen 2011	51.93	7.66	125	52.62	5.98	125	100.0%	-0.69 [-2.39, 1.01]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-0.69 [-2.39, 1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.79 (P = 0.43)								
4.3.2 RF								
Rasmussen 2011	51.93	7.66	125	53.23	5.32	125	100.0%	-1.30 [-2.93, 0.33]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-1.30 [-2.93, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.56 (P = 0.12)								

Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%

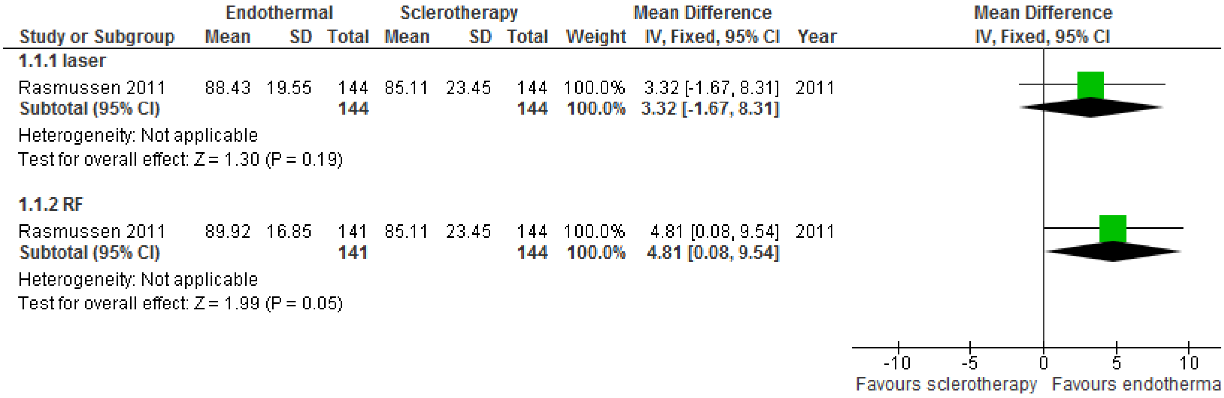
Figure 123: Foam sclerotherapy vs. endothermal ablation: SF-36 mental 1 year



	sclerotherapy			endothermal				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
4.4.1 Laser								
Rasmussen 2011	54.73	8.89	125	56.74	5.44	125	100.0%	-2.01 [-3.84, -0.18]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-2.01 [-3.84, -0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.16 (P = 0.03)								
4.4.2 RF								
Rasmussen 2011	54.73	8.89	125	56.52	6.17	125	100.0%	-1.79 [-3.69, 0.11]
Subtotal (95% CI)			**125**			**125**	**100.0%**	**-1.79 [-3.69, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.85 (P = 0.06)								

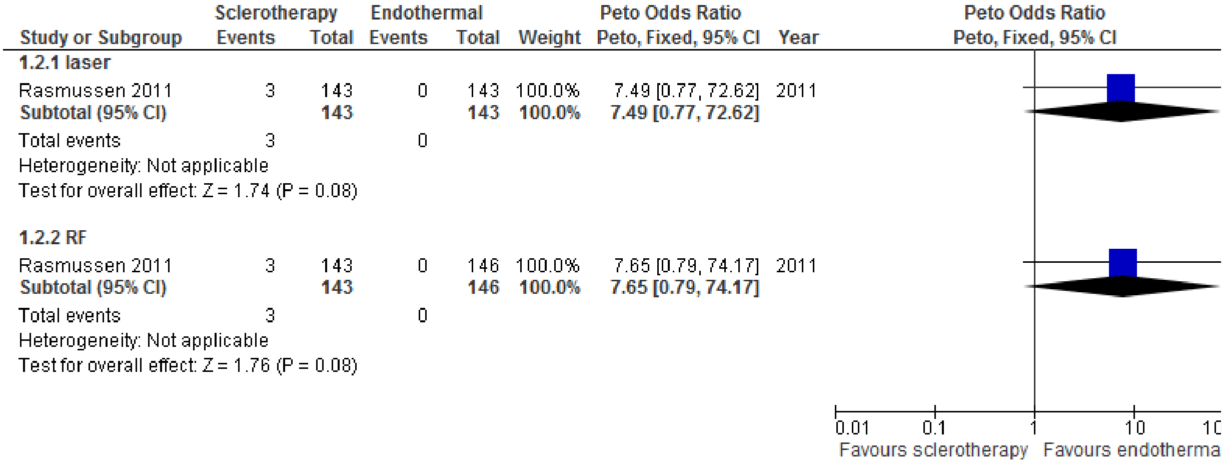
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%

Figure 124: Foam sclerotherapy vs. endothermal ablation: Pain due to varicose veins (1 year) (higher better as taken from SF-36 sub-scale)



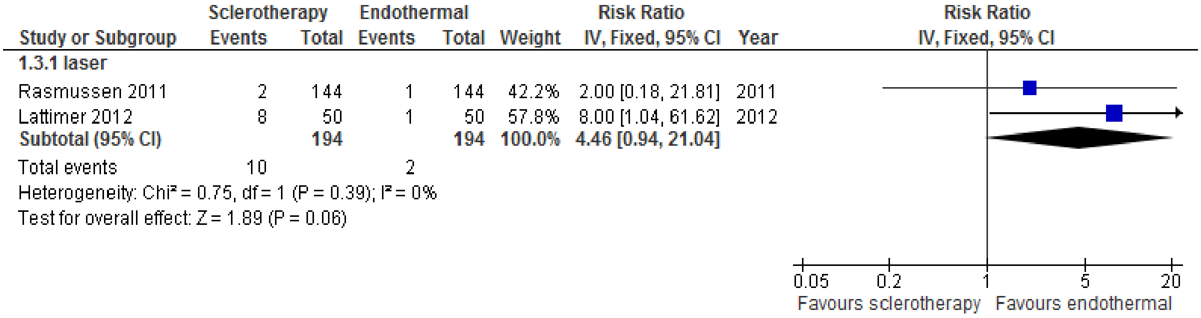
	Endothermal			Sclerotherapy				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
1.1.1 laser									
Rasmussen 2011	88.43	19.55	144	85.11	23.45	144	100.0%	3.32 [-1.67, 8.31]	2011
Subtotal (95% CI)			**144**			**144**	**100.0%**	**3.32 [-1.67, 8.31]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.30 (P = 0.19)									
1.1.2 RF									
Rasmussen 2011	89.92	16.85	141	85.11	23.45	144	100.0%	4.81 [0.08, 9.54]	2011
Subtotal (95% CI)			**141**			**144**	**100.0%**	**4.81 [0.08, 9.54]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.99 (P = 0.05)									

Figure 125: Foam sclerotherapy vs. endothermal ablation: Reflux above knee at 3 days



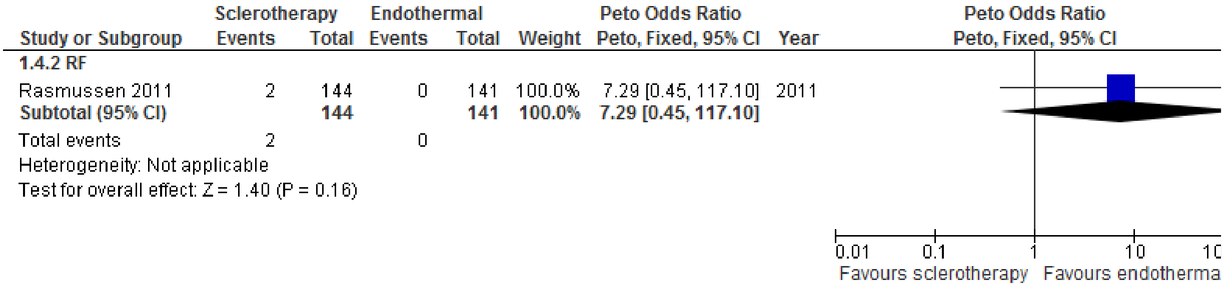
	Sclerotherapy		Endothermal			Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year
1.2.1 laser							
Rasmussen 2011	3	143	0	143	100.0%	7.49 [0.77, 72.62]	2011
Subtotal (95% CI)		**143**		**143**	**100.0%**	**7.49 [0.77, 72.62]**	
Total events	3		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.74 (P = 0.08)							
1.2.2 RF							
Rasmussen 2011	3	143	0	146	100.0%	7.65 [0.79, 74.17]	2011
Subtotal (95% CI)		**143**		**146**	**100.0%**	**7.65 [0.79, 74.17]**	
Total events	3		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.76 (P = 0.08)							

Figure 126: Foam sclerotherapy vs. endothermal ablation (Laser):Reflux above knee at 3-4 weeks



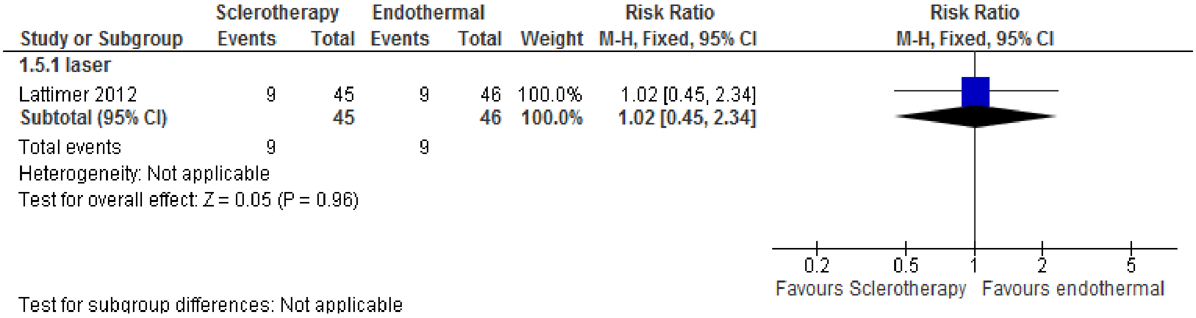
	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	Year
1.3.1 laser							
Rasmussen 2011	2	144	1	144	42.2%	2.00 [0.18, 21.81]	2011
Lattimer 2012	8	50	1	50	57.8%	8.00 [1.04, 61.62]	2012
Subtotal (95% CI)		**194**		**194**	**100.0%**	**4.46 [0.94, 21.04]**	
Total events	10		2				
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 1.89 (P = 0.06)							

Figure 127: Foam sclerotherapy vs. endothermal ablation (RF): Reflux above knee at 1 month



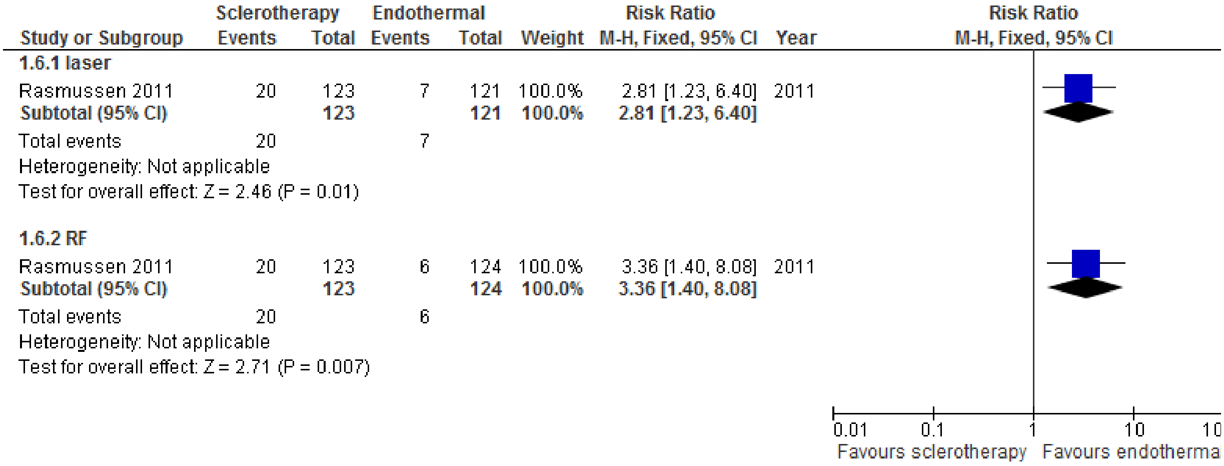
	Sclerotherapy		Endothermal			Peto Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**Peto, Fixed, 95% CI**	**Year**
1.4.2 RF							
Rasmussen 2011	2	144	0	141	100.0%	7.29 [0.45, 117.10]	2011
Subtotal (95% CI)		**144**		**141**	**100.0%**	**7.29 [0.45, 117.10]**	
Total events	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.40 (P = 0.16)							

Figure 128: Foam sclerotherapy vs. endothermal ablation(Laser): Reflux above knee at 3 months



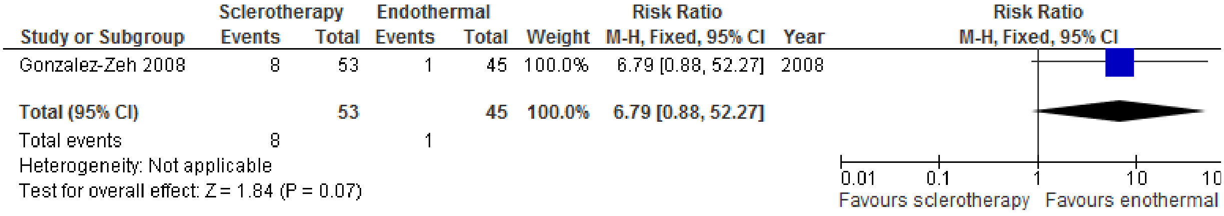
	Sclerotherapy		Endothermal			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.5.1 laser						
Lattimer 2012	9	45	9	46	100.0%	1.02 [0.45, 2.34]
Subtotal (95% CI)		**45**		**46**	**100.0%**	**1.02 [0.45, 2.34]**
Total events	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Not applicable						

Figure 129: Foam sclerotherapy vs. endothermal ablation: Reflux above knee 1 year



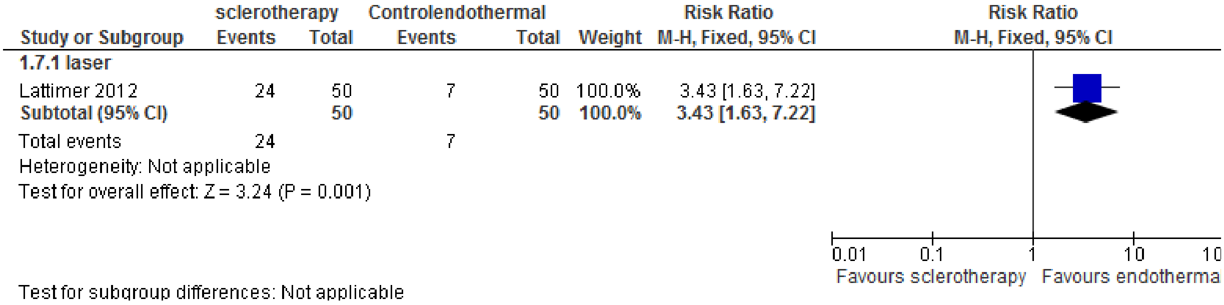
	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
1.6.1 laser							
Rasmussen 2011	20	123	7	121	100.0%	2.81 [1.23, 6.40]	2011
Subtotal (95% CI)		**123**		**121**	**100.0%**	**2.81 [1.23, 6.40]**	
Total events	20		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.46 (P = 0.01)							
1.6.2 RF							
Rasmussen 2011	20	123	6	124	100.0%	3.36 [1.40, 8.08]	2011
Subtotal (95% CI)		**123**		**124**	**100.0%**	**3.36 [1.40, 8.08]**	
Total events	20		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.71 (P = 0.007)							

Figure 130: Foam sclerotherapy vs. endothermal ablation: Reflux at 1 year observational data



	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Gonzalez-Zeh 2008	8	53	1	45	100.0%	6.79 [0.88, 52.27]	2008
Total (95% CI)		**53**		**45**	**100.0%**	**6.79 [0.88, 52.27]**	
Total events	8		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.84 (P = 0.07)							

Figure 131: Foam sclerotherapy vs. endothermal ablation: Reflux below knee 3 weeks

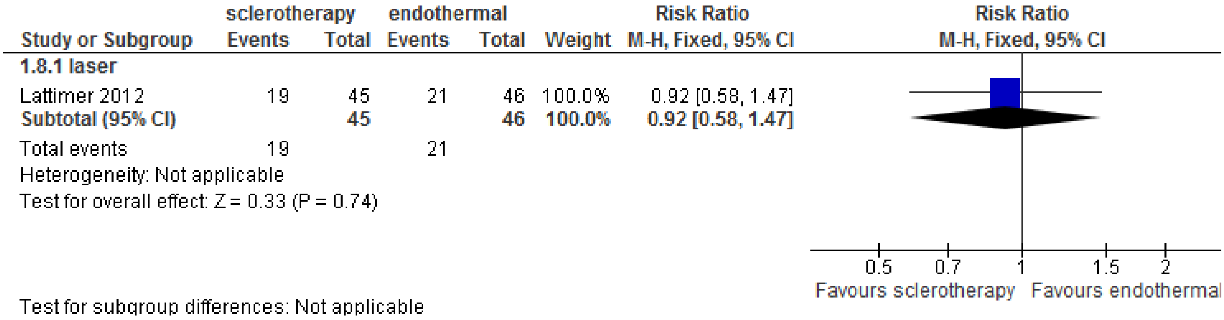


	sclerotherapy		Controlendothermal			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.7.1 laser						
Lattimer 2012	24	50	7	50	100.0%	3.43 [1.63, 7.22]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**3.43 [1.63, 7.22]**
Total events	24		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.24 (P = 0.001)

Test for subgroup differences: Not applicable

Figure 132: Foam sclerotherapy vs. endothermal ablation: Reflux below knee 3 months

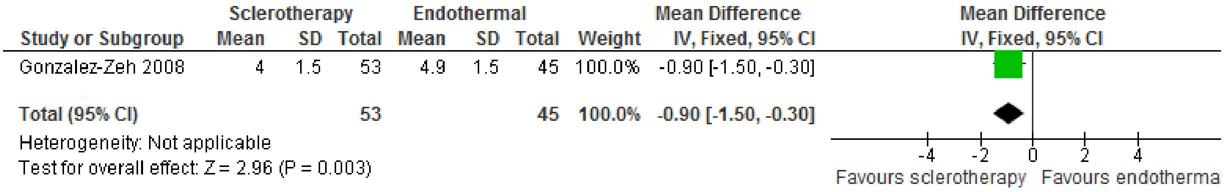


	sclerotherapy		endothermal			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.8.1 laser						
Lattimer 2012	19	45	21	46	100.0%	0.92 [0.58, 1.47]
Subtotal (95% CI)		**45**		**46**	**100.0%**	**0.92 [0.58, 1.47]**
Total events	19		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

Test for subgroup differences: Not applicable

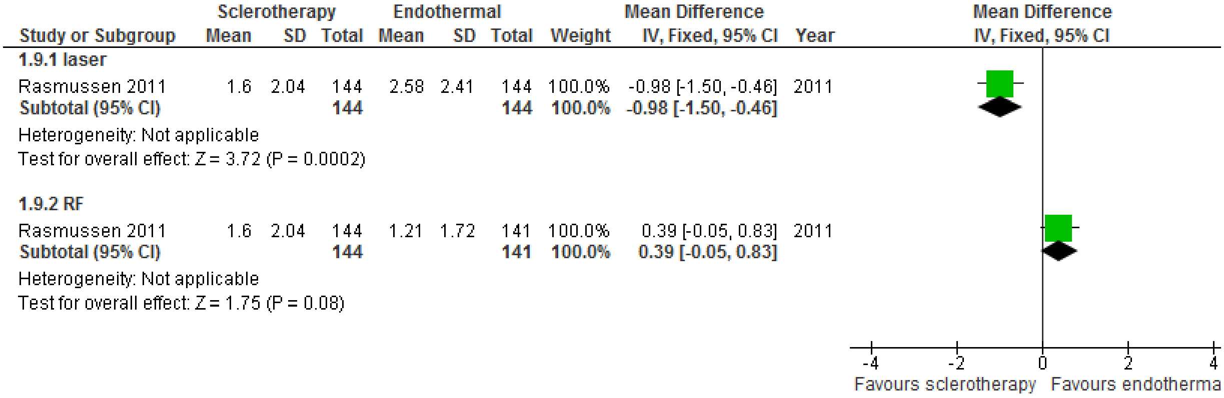
Figure 133: Foam sclerotherapy vs. endothermal ablation: Adverse events – pain (VAS) observational data



	Sclerotherapy			Endothermal				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Gonzalez-Zeh 2008	4	1.5	53	4.9	1.5	45	100.0%	-0.90 [-1.50, -0.30]
Total (95% CI)			**53**			**45**	**100.0%**	**-0.90 [-1.50, -0.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.96 (P = 0.003)

Figure 134: Foam sclerotherapy vs. endothermal ablation: Adverse events – post op pain 10 days

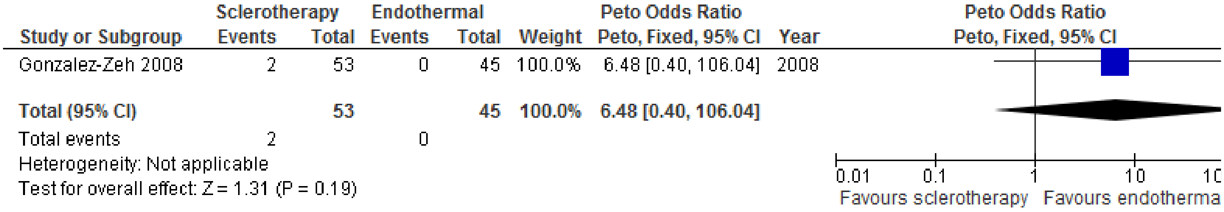


	Sclerotherapy			Endothermal				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
1.9.1 laser									
Rasmussen 2011	1.6	2.04	144	2.58	2.41	144	100.0%	-0.98 [-1.50, -0.46]	2011
Subtotal (95% CI)			**144**			**144**	**100.0%**	**-0.98 [-1.50, -0.46]**	
1.9.2 RF									
Rasmussen 2011	1.6	2.04	144	1.21	1.72	141	100.0%	0.39 [-0.05, 0.83]	2011
Subtotal (95% CI)			**144**			**141**	**100.0%**	**0.39 [-0.05, 0.83]**	

1.9.1 laser: Heterogeneity: Not applicable
Test for overall effect: Z = 3.72 (P = 0.0002)

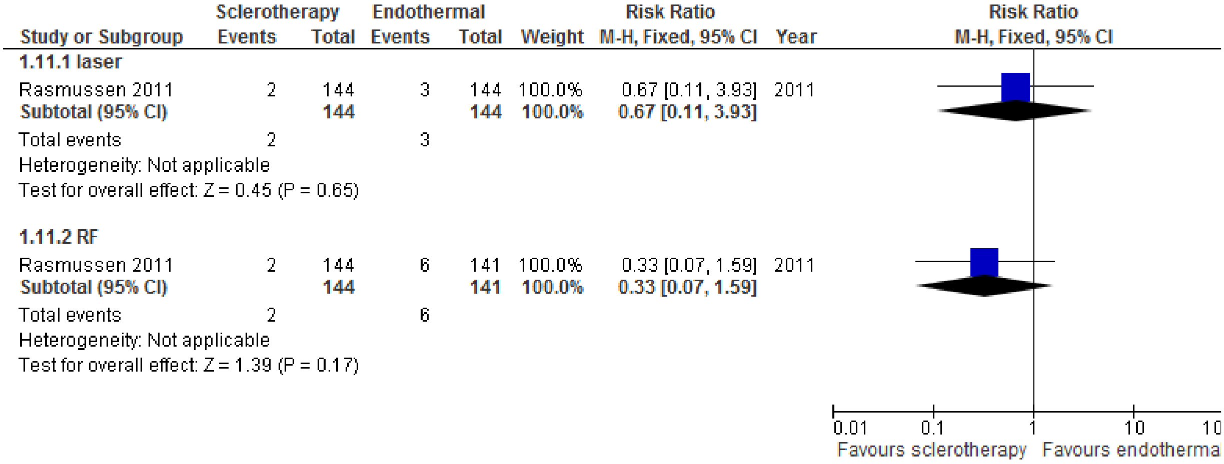
1.9.2 RF: Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

Figure 135: Foam sclerotherapy vs. endothermal ablation: Adverse events – DVT observational data



	Sclerotherapy		Endothermal			Peto Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**Peto, Fixed, 95% CI**	**Year**
Gonzalez-Zeh 2008	2	53	0	45	100.0%	6.48 [0.40, 106.04]	2008
Total (95% CI)		**53**		**45**	**100.0%**	**6.48 [0.40, 106.04]**	
Total events	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.31 (P = 0.19)							

Figure 136: Foam sclerotherapy vs. endothermal ablation: Adverse events – neural injury/damage

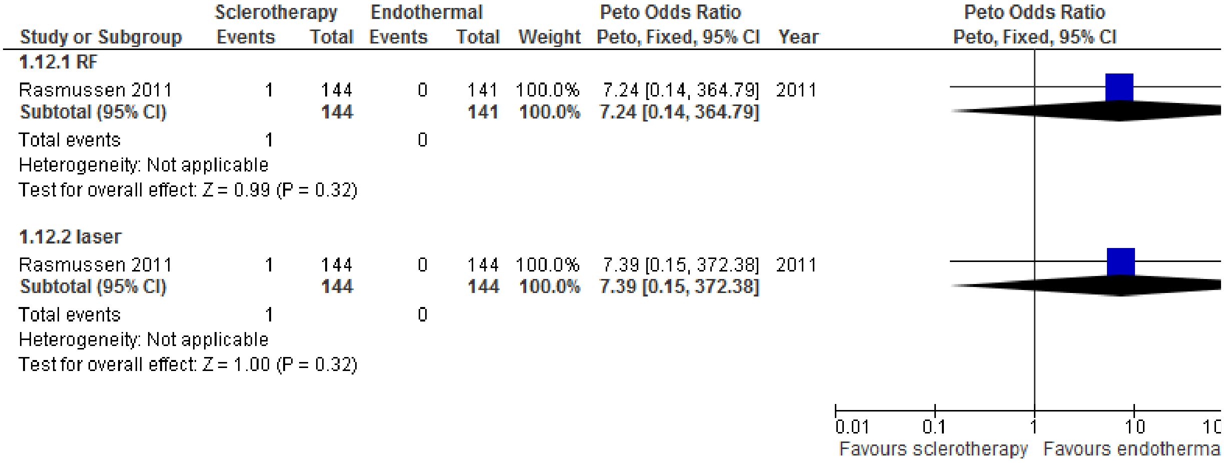


	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
1.11.1 laser							
Rasmussen 2011	2	144	3	144	100.0%	0.67 [0.11, 3.93]	2011
Subtotal (95% CI)		**144**		**144**	**100.0%**	**0.67 [0.11, 3.93]**	
Total events	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.45 (P = 0.65)							
1.11.2 RF							
Rasmussen 2011	2	144	6	141	100.0%	0.33 [0.07, 1.59]	2011
Subtotal (95% CI)		**144**		**141**	**100.0%**	**0.33 [0.07, 1.59]**	
Total events	2		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.39 (P = 0.17)							

Figure 137: Foam sclerotherapy vs. endothermal ablation: Adverse events – paraesthesia observational data

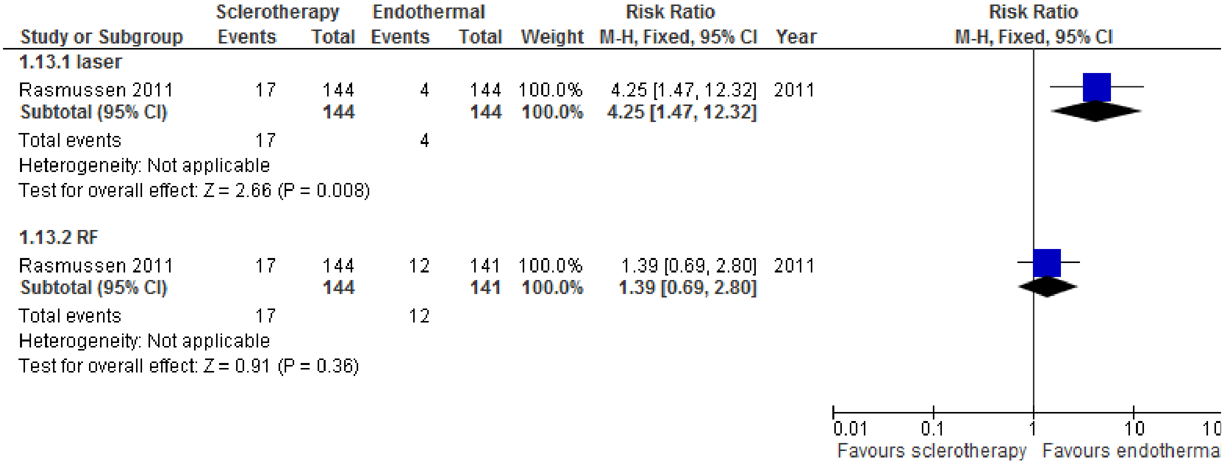
	Sclerotherapy		Endothermal			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Gonzalez-Zeh 2008	1	53	2	45	100.0%	0.42 [0.04, 4.53]
Total (95% CI)		**53**		**45**	**100.0%**	**0.42 [0.04, 4.53]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						

Figure 138: Foam sclerotherapy vs. endothermal ablation: Adverse events PE



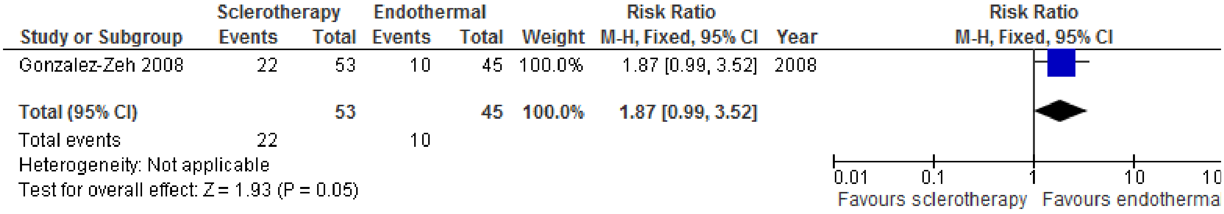
	Sclerotherapy		Endothermal			Peto Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**Peto, Fixed, 95% CI**	**Year**
1.12.1 RF							
Rasmussen 2011	1	144	0	141	100.0%	7.24 [0.14, 364.79]	2011
Subtotal (95% CI)		**144**		**141**	**100.0%**	**7.24 [0.14, 364.79]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
1.12.2 laser							
Rasmussen 2011	1	144	0	144	100.0%	7.39 [0.15, 372.38]	2011
Subtotal (95% CI)		**144**		**144**	**100.0%**	**7.39 [0.15, 372.38]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.00 (P = 0.32)							

Figure 139: Foam sclerotherapy vs. endothermal ablation: Adverse events – Phlebitis



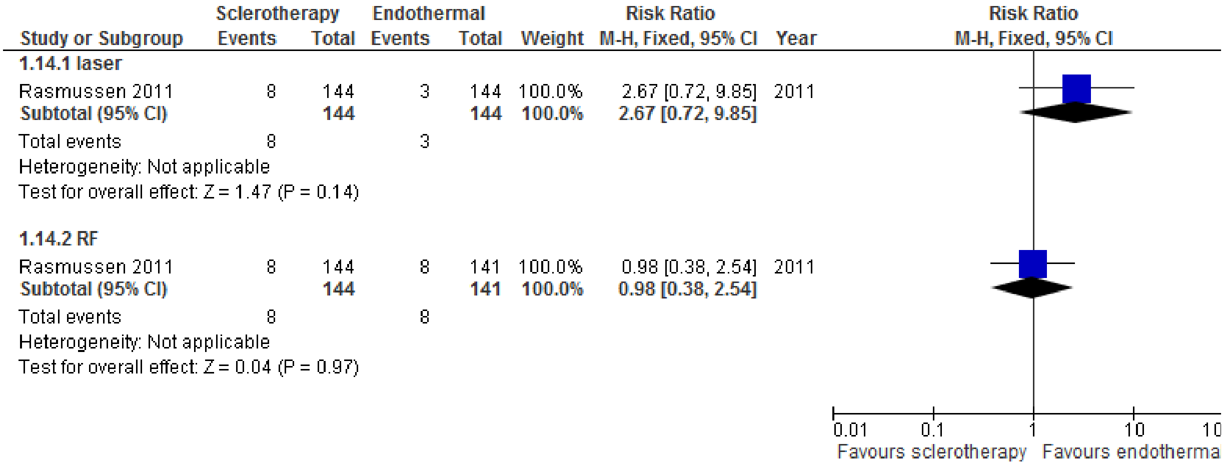
	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
1.13.1 laser							
Rasmussen 2011	17	144	4	144	100.0%	4.25 [1.47, 12.32]	2011
Subtotal (95% CI)		**144**		**144**	**100.0%**	**4.25 [1.47, 12.32]**	
Total events	17		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.66 (P = 0.008)							
1.13.2 RF							
Rasmussen 2011	17	144	12	141	100.0%	1.39 [0.69, 2.80]	2011
Subtotal (95% CI)		**144**		**141**	**100.0%**	**1.39 [0.69, 2.80]**	
Total events	17		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							

Figure 140: Foam sclerotherapy vs. endothermal ablation: Adverse events – Phlebitis observational data



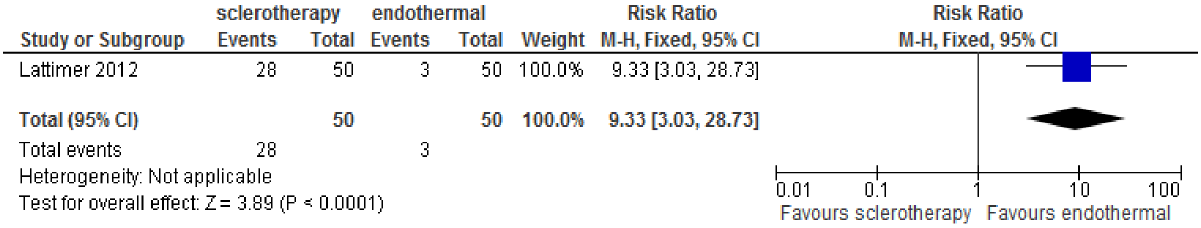
	Sclerotherapy		Endothermal			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Gonzalez-Zeh 2008	22	53	10	45	100.0%	1.87 [0.99, 3.52]	2008
Total (95% CI)		**53**		**45**	**100.0%**	**1.87 [0.99, 3.52]**	
Total events	22		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.93 (P = 0.05)							

Figure 141: Foam sclerotherapy vs. endothermal ablation: Adverse events – hyper-pigmentation



Study or Subgroup	Sclerotherapy Events	Sclerotherapy Total	Endothermal Events	Endothermal Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.14.1 laser							
Rasmussen 2011	8	144	3	144	100.0%	2.67 [0.72, 9.85]	2011
Subtotal (95% CI)		**144**		**144**	**100.0%**	**2.67 [0.72, 9.85]**	
Total events	8		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							
1.14.2 RF							
Rasmussen 2011	8	144	8	141	100.0%	0.98 [0.38, 2.54]	2011
Subtotal (95% CI)		**144**		**141**	**100.0%**	**0.98 [0.38, 2.54]**	
Total events	8		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							

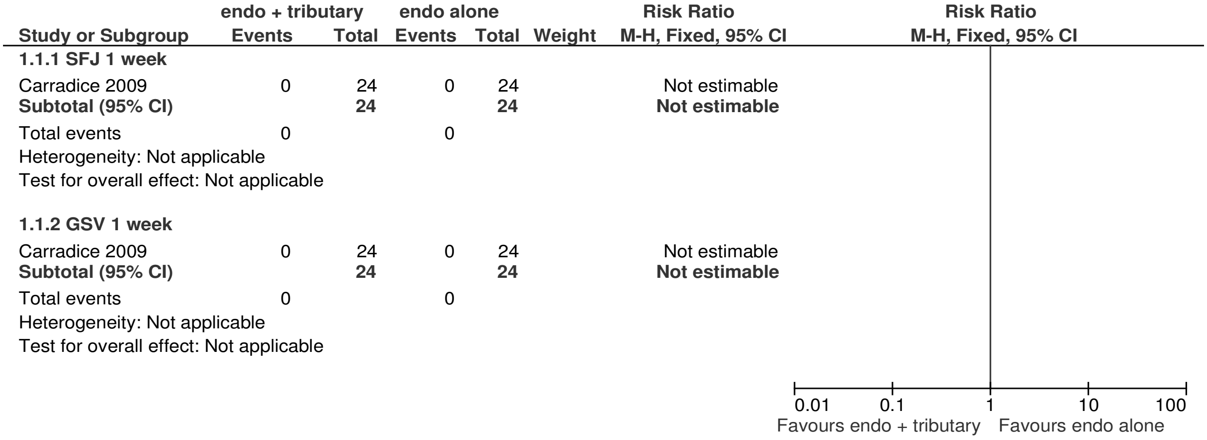
Figure 142: Foam sclerotherapy vs. endothermal ablation(Laser): Need for further treatment



Study or Subgroup	sclerotherapy Events	sclerotherapy Total	endothermal Events	endothermal Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lattimer 2012	28	50	3	50	100.0%	9.33 [3.03, 28.73]
Total (95% CI)		**50**		**50**	**100.0%**	**9.33 [3.03, 28.73]**
Total events	28		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.89 (P < 0.0001)						

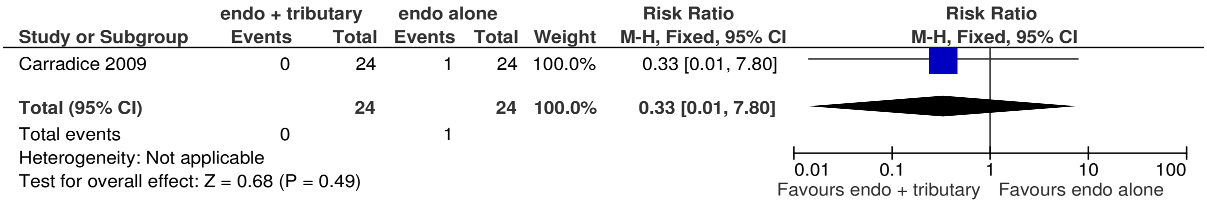
I.3.4 Truncal treatment with tributary treatment vs. truncal treatment alone

Figure 143: Truncal + tributary vs. truncal alone: Reflux at one week



Study or Subgroup	endo + tributary Events	endo + tributary Total	endo alone Events	endo alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 SFJ 1 week						
Carradice 2009	0	24	0	24		Not estimable
Subtotal (95% CI)		**24**		**24**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 GSV 1 week						
Carradice 2009	0	24	0	24		Not estimable
Subtotal (95% CI)		**24**		**24**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

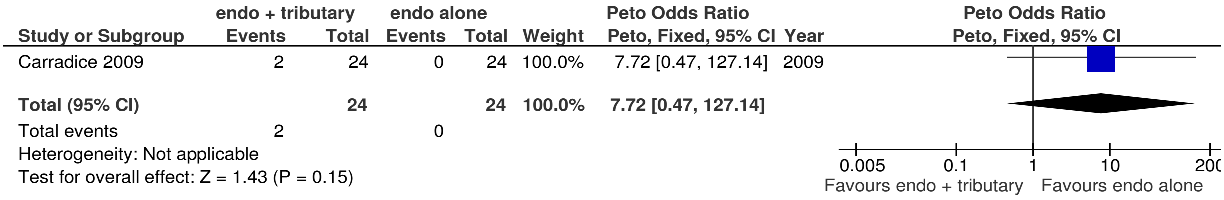
Figure 144: Truncal + tributary vs. truncal alone: Adverse events - phlebitis



	endo + tributary		endo alone			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Carradice 2009	0	24	1	24	100.0%	0.33 [0.01, 7.80]
Total (95% CI)		**24**		**24**	**100.0%**	**0.33 [0.01, 7.80]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)

Figure 145: Truncal + tributary vs. truncal alone: Adverse events - pigmentation

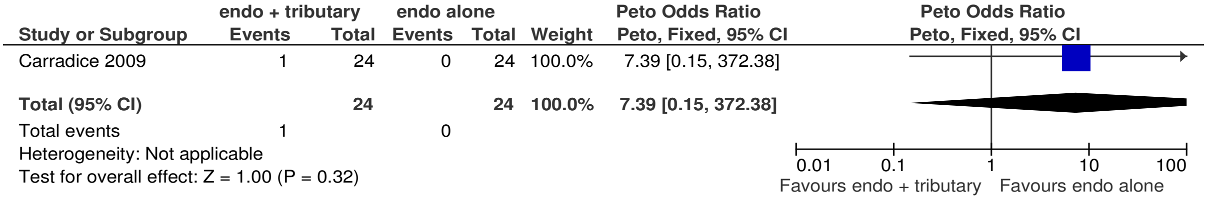


	endo + tributary		endo alone			Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year
Carradice 2009	2	24	0	24	100.0%	7.72 [0.47, 127.14]	2009
Total (95% CI)		**24**		**24**	**100.0%**	**7.72 [0.47, 127.14]**	
Total events	2		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

Source: <Insert Source text here>

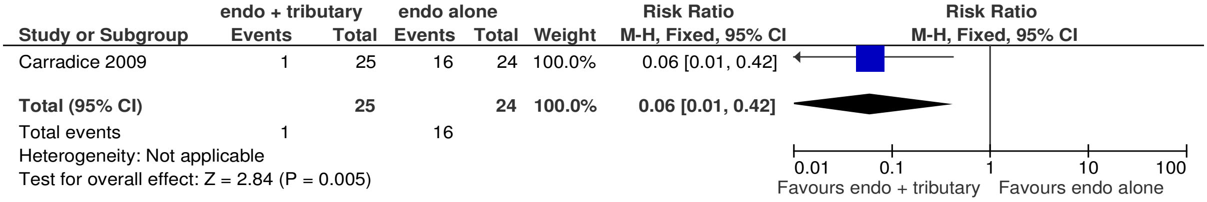
Figure 146: Truncal + tributary vs. truncal alone: Adverse events – thigh neuralgia



	endo + tributary		endo alone			Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI
Carradice 2009	1	24	0	24	100.0%	7.39 [0.15, 372.38]
Total (95% CI)		**24**		**24**	**100.0%**	**7.39 [0.15, 372.38]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

Figure 147: Truncal + tributary vs. truncal alone: Need for ambulatory phlebectomy at 6 weeks



	endo + tributary		endo alone			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Carradice 2009	1	25	16	24	100.0%	0.06 [0.01, 0.42]
Total (95% CI)		**25**		**24**	**100.0%**	**0.06 [0.01, 0.42]**
Total events	1		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.84 (P = 0.005)

1 # I.4 Chapter 10 – compression after interventional treatment

2 ## I.4.1.1 Compression after surgery vs. surgery alone

Figure 148: Compression after interventional treatment vs. interventional treatment alone: adverse events – post operative pain (higher worse)

	surg with comp			surg alone				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**Year**
1.1.1 3 days									
Houtermans-Auckel 2009	2.5	2.8	46	1.8	2.2	50	100.0%	0.70 [-0.31, 1.71]	2009
Subtotal (95% CI)			**46**			**50**	**100.0%**	**0.70 [-0.31, 1.71]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.35 (P = 0.18)									
1.1.2 2 weeks									
Houtermans-Auckel 2009	2.2	2.3	46	2.2	2.4	50	100.0%	0.00 [-0.94, 0.94]	2009
Subtotal (95% CI)			**46**			**50**	**100.0%**	**0.00 [-0.94, 0.94]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
1.1.3 4 weeks									
Houtermans-Auckel 2009	0.8	1.5	46	0.5	0.8	50	100.0%	0.30 [-0.19, 0.79]	2009
Subtotal (95% CI)			**46**			**50**	**100.0%**	**0.30 [-0.19, 0.79]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.21 (P = 0.23)									

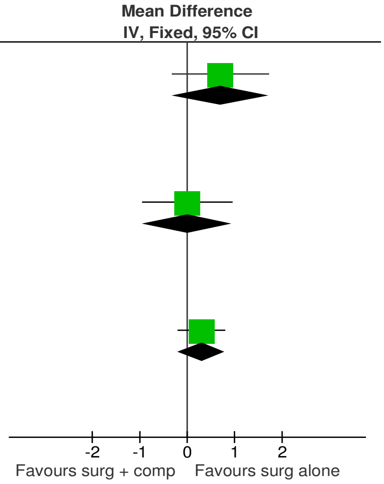


Figure 149: Compression after interventional treatment vs. interventional treatment alone: adverse events - numbness

	surg with comp		surg alone			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
1.2.1 3 days							
Houtermans-Auckel 2009	4	46	3	50	100.0%	1.45 [0.34, 6.13]	2009
Subtotal (95% CI)		**46**		**50**	**100.0%**	**1.45 [0.34, 6.13]**	
Total events	4		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.50 (P = 0.61)							
1.2.2 2 weeks							
Houtermans-Auckel 2009	0	46	2	50	100.0%	0.22 [0.01, 4.40]	2009
Subtotal (95% CI)		**46**		**50**	**100.0%**	**0.22 [0.01, 4.40]**	
Total events	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
1.2.3 4 weeks							
Houtermans-Auckel 2009	0	46	0	50		Not estimable	2009
Subtotal (95% CI)		**46**		**50**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

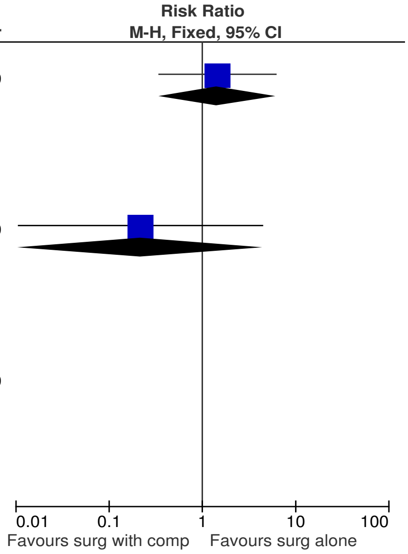
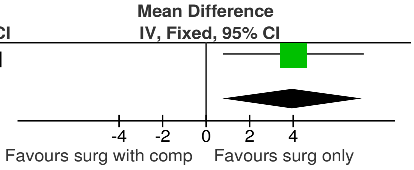


Figure 150: Compression after interventional treatment vs. interventional treatment alone: return to work (days)

	surg with comp			surg alone				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Houtermans-Auckel 2009	15	8.4	46	11	7.5	50	100.0%	4.00 [0.80, 7.20]
Total (95% CI)			**46**			**50**	**100.0%**	**4.00 [0.80, 7.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.45 (P = 0.01)								



I.4.1.2 Compression after foam sclerotherapy vs. foam sclerotherapy alone

Figure 151: Compression after interventional treatment vs. interventional treatment alone: QoL – CIVIQ global score – change from baseline (greater negative change is better)

	sclero + comp			sclero alone				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
2.1.1 14 days									
Hamel-Desnos 2010	-5.5	10	22	-9	9.9	21	100.0%	3.50 [-2.45, 9.45]	2010
Subtotal (95% CI)			**22**			**21**	**100.0%**	**3.50 [-2.45, 9.45]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.15 (P = 0.25)									
2.1.2 28 days									
Hamel-Desnos 2010	-9.4	10	23	-11	14	24	100.0%	1.60 [-5.33, 8.53]	2010
Subtotal (95% CI)			**23**			**24**	**100.0%**	**1.60 [-5.33, 8.53]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.45 (P = 0.65)									

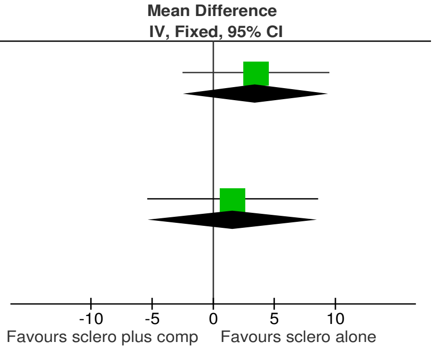


Figure 152: Compression after interventional treatment vs. interventional treatment alone: reflux at 28 days

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Hamel-Desnos 2010	0	31	0	29		Not estimable
Total (95% CI)		**31**		**29**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

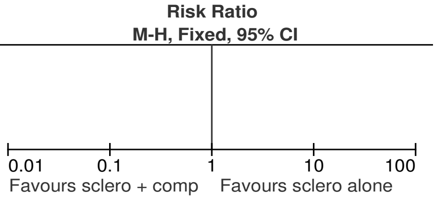


Figure 153: Compression after interventional treatment vs. interventional treatment alone: adverse events – major neurological events

	sclero + comp		sclero alone			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Hamel-Desnos 2010	0	31	0	29		Not estimable	2010
Total (95% CI)		**31**		**29**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

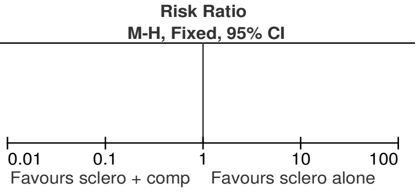


Figure 154: Compression after interventional treatment vs. interventional treatment alone: adverse events – visual disturbance (scotoma) resolving within 15 minutes

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Hamel-Desnos 2010	0	31	1	29	100.0%	0.31 [0.01, 7.38]
Total (95% CI)		**31**		**29**	**100.0%**	**0.31 [0.01, 7.38]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						

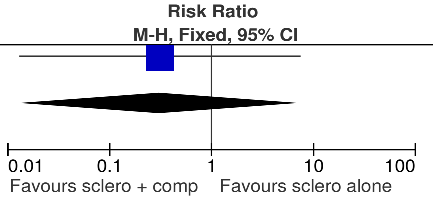


Figure 155: Compression after interventional treatment vs. interventional treatment alone: adverse events – moderate pain day 28

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Hamel-Desnos 2010	1	30	3	29	100.0%	0.32 [0.04, 2.92]
Total (95% CI)		**30**		**29**	**100.0%**	**0.32 [0.04, 2.92]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

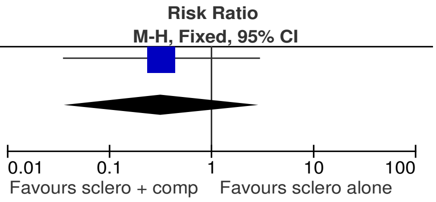


Figure 156: Compression after interventional treatment vs. interventional treatment alone: adverse events - pigmentation

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Hamel-Desnos 2010	2	30	1	29	100.0%	1.93 [0.19, 20.18]
Total (95% CI)		**30**		**29**	**100.0%**	**1.93 [0.19, 20.18]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)

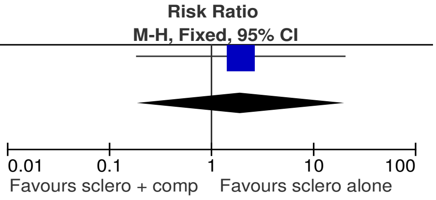


Figure 157: Compression after interventional treatment vs. interventional treatment alone: adverse events - thrombophlebitis

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Hamel-Desnos 2010	3	30	3	29	100.0%	0.97 [0.21, 4.41]
Total (95% CI)		**30**		**29**	**100.0%**	**0.97 [0.21, 4.41]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

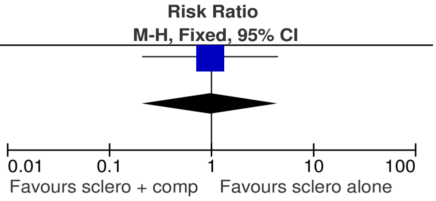
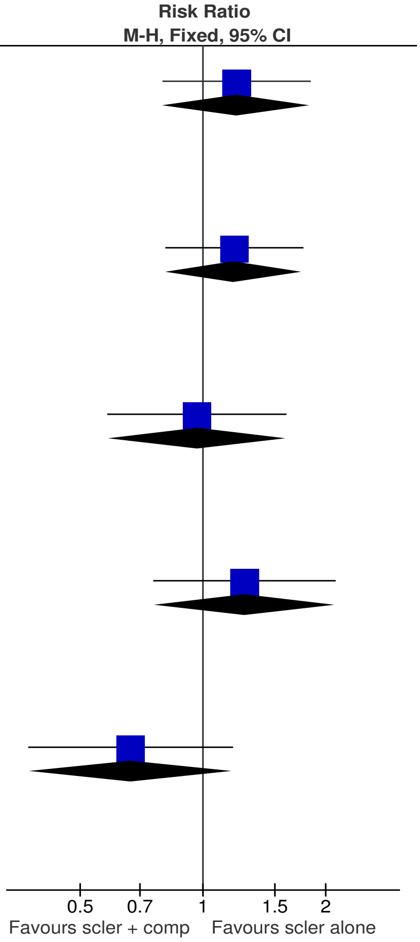


Figure 158: Compression after interventional treatment vs. interventional treatment alone: patient assessed symptoms

	sclero + comp		sclero alone			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
2.8.1 heavy legs						
Hamel-Desnos 2010	20	30	16	29	100.0%	1.21 [0.80, 1.83]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**1.21 [0.80, 1.83]**
Total events	20		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.8.2 pain						
Hamel-Desnos 2010	21	30	17	29	100.0%	1.19 [0.81, 1.76]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**1.19 [0.81, 1.76]**
Total events	21		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.8.3 oedema						
Hamel-Desnos 2010	15	30	15	29	100.0%	0.97 [0.59, 1.60]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**0.97 [0.59, 1.60]**
Total events	15		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
2.8.4 paraesthesia						
Hamel-Desnos 2010	17	30	13	29	100.0%	1.26 [0.76, 2.11]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**1.26 [0.76, 2.11]**
Total events	17		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.8.5 cramp						
Hamel-Desnos 2010	11	30	16	29	100.0%	0.66 [0.37, 1.18]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**0.66 [0.37, 1.18]**
Total events	11		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						



Appendix J: Excluded clinical studies

J.1 Chapter 5 – patient perceptions and expectations

Table 98: Studies excluded from the clinical review for chapter 5

Reference	Reason for exclusion
Bradshaw 1999[31]	Does not match the review question
Ching 2010[56]	Only covered new Zealand-based websites and so not relevant to the UK
Davies 1995[68]	Does not match the review question
Murphy 2001[179]	This paper was deemed too old for its survey of internet information to have any continued relevance.
Sains 2005[235]	Does not match the review question
Scurr 2008[243]	Does not match the review question
Srilekha 2005[254]	Does not match the review question

J.2 Chapter 6 – referral to a vascular service

J.2.1 Risk factors associated with disease progression

Table 99: Studies excluded from the clinical review: risk factors associated with disease progression

Reference	Reason for exclusion
Bernardini, 2010[22]	No relevant outcomes and also does not match review question
Brand, 1988[32]	No relevant outcomes and also does not match review question
Carpentier, 2008[45]	Abstract. Authors contacted for more information but no reply received.
Christenson, 2012[58]	Abstract. Authors contacted for more information but no reply received.
Cushman, 2010 [63]	No relevant outcomes and also does not match review question
Diamond, 2012[78]	No relevant outcomes and also does not match review question Abstract only
Dzieciuchowicz, 2011[91]	Incorrect study design (cross-sectional)
Gasparis, 2008 [101]	No relevant outcomes and also does not match review question Abstract only
Kostas, 2010[138]	No relevant outcomes and also does not match review question
Labropoulos, 2012[142]	No relevant outcomes and also does not match review question
Mackenzie, 2003 [155]	No relevant outcomes and also does not match review question
McLafferty, 2009 [162]	Abstract. Authors contacted for more information but no reply received.
Moore, 2011[172]	Incorrect study design (cross-sectional) Abstract only
Pannier, 2012[203]	No relevant outcomes and also does not match review question Abstract only
Mota-Capitao, 1995[175]	Incorrect study design - a cross-sectional study rather than a case control or

Reference	Reason for exclusion
	prospective cohort study
Rabe, 2010[216]	Incorrect study design (commentary)
Robertson, 2011[229]	No relevant outcomes and also does not match review question Abstract only
Treiman, 2001[271]	No relevant outcomes and also does not match review question
Uhl, 2005[274]	Incorrect study design - a cross-sectional study rather than a case control or prospective cohort study

J.2.2 Factors associated with better/worse response to treatment

Table 100: Studies excluded from the clinical review: Factors associated with better/worse response to treatment

Ref ID	Reason for exclusion
Ali, 2007[5]	No relevant outcomes and does not match review question
Allegra, 2007 [6]	Incorrect study design - no multivariable analysis
Atkin, 2007[10]	Incorrect study design - no multivariable analysis
Barrett, 2004[12]	Incorrect study design - no multivariable analysis
Bush, 2012[38]	Abstract only
Calcagno, 2009[39]	Incorrect study design - no multivariable analysis
Carradice, 2011[48]	No relevant outcomes and does not match review question
Chaar, 2011[51]	Incorrect study design - retrospective
Chi, 2011[55]	Abstract only
Ciostek, 2004[59]	Incorrect study design - no multivariable analysis
Corbett, 2011[61]	Incorrect study design - no multivariable analysis Abstract only
Defty, 2008[74]	Incorrect study design - no multivariable analysis
Einarsson, 1993[94]	Intervention does not match protocol (liquid sclerotherapy)
Goode, 2009[108]	No relevant outcomes and does not match review question
Hartmann, 2006[112]	Incorrect study design - no multivariable analysis
Hingorani, 2009[115]	Intervention does not match protocol
Jagtman, 2003[123]	Intervention does not match protocol - liquid sclerotherapy
Kakkos, 2006[128]	Incorrect study design - no multivariable analysis for the analysis frelevant to the review question
Kim, 2006[133]	Incorrect study design - no multivariable analysis
Magnusson, 2006[157]	Incorrect study design – retrospective study
Marsh, 2010[160]	Incorrect study design - no multivariable analysis
Marston, 2008[161]	Incorrect study design - no multivariable analysis
Meissner, 2012[164]	Abstract only
Miyazaki, 2005[171]	Incorrect study design – retrospective study
Mouton, 2008[177]	Population does not match protocol - inguinal varices
Nash, 1991[181]	Incorrect study design - no multivariable analysis
Nelzen, 2010[183]	Abstract only
Oguzkurt, 2010[192]	Abstract only

Ref ID	Reason for exclusion
Ozsvath, 2010[196]	Abstract only
Pittaluga, 2009[211]	Incorrect study design - no multivariable analysis
Pittaluga, 2012[210]	No relevant outcomes and does not match review question
Puggioni, 2005[214]	Incorrect study design - no multivariable analysis
Puggioni, 2009[215]	Incorrect study design - no multivariable analysis
Sarvananthan, 2012[237]	Incorrect study design - no multivariable analysis
Shepherd, 2009[246]	Abstract only
Shepherd, 2010[245]	Multivariable analysis, considering confounders such as sex, BMI or clinical disease severity, but no report of the independent effects of each confounder.
Stother, 1974[255]	intervention does not match protocol (liquid sclerotherapy)
Tzilinis, 2005[273]	Incorrect study design - no multivariable analysis
Van Neer, 2006[277]	Incorrect study design - no multivariable analysis
Vandy, 2011[278]	Abstract only
Ward, 2011[280]	Abstract only
Wright, 2006[285]	Incorrect study design - no multivariable analysis
Zamboni, 2010[289]	Incorrect study design - no multivariable analysis

J.3 Chapter 7 – assessment for treatment

J.3.1 Diagnostic assessment of hand held Doppler

Table 101: Studies excluded from the clinical review: diagnostic assessment of hand held Doppler

Author/title	Reason for exclusion
Antoch 2002[8]	Does not address diagnostic accuracy
Campbell 2005[43]	No diagnostic data presented
Dixon 1996[88]	Does not address diagnostic accuracy
Engel 1991[95]	Does not address diagnostic accuracy
Olivienca 1998[194]	Does not address diagnostic accuracy
Phillips 1995[205]	No HHD diagnostic data
Pierik 1997[209]	No HHD diagnostic data
Singh 1997[250]	No usable diagnostic data presented
Yamaki 2002[288]	Does not address diagnostic accuracy

J.3.2 Duplex assessment prior to treatment

Table 102: Studies excluded from the clinical review

Ref ID	Reason for exclusion
Campbell 1996[42]	No relevant outcomes and does not match review question
Cavezzi 2000[49]	Comparator does not match protocol - no comparator
Cavezzi 2007[50]	No relevant outcomes and does not match review question
Coleridge-Smith 2007[60]	No relevant outcomes and does not match review question

Ref ID	Reason for exclusion
De Maeseneer 2011[69]	No relevant outcomes and does not match review question
Krodowicz 2010[136]	No relevant outcomes and does not match review question
Levi 1995[145]	Population does not match protocol - population were patients undergoing infrainguinal bypass procedures; Comparator does not match protocol - no comparator
Makris 2006 [158]	No relevant outcomes and does not match review question
Pachler 1998[197]	Comparator does not match protocol - no comparator
Pichot 2000[208]	Comparator does not match protocol - no comparator
Pleass 1996[212]	No relevant outcomes and does not match review question
Safar 2004[234]	Comparator does not match protocol - no comparator
Somjen 1996[253]	No relevant outcomes and does not match review question
Campbell 1996[42]	No relevant outcomes and does not match review question
Oinonen 2007[193]	No relevant outcomes and does not match review question - both Duplex and hand held doppler were both used for pre-op marking, with some patients only having been examined with HHD. Also, all patients had a duplex/doppler assessment, the difference between groups being that in one group the duplex/doppler findings were only communicated to the surgeons in written form, whereas in the other group the surgeon was allowed to do a pre-op marking, by utilising HHD and the previous duplex/doppler findings.

J.4 Chapter 8 – conservative management

J.4.1 Compression vs. no treatment

Table 103: List of excluded studies

Reference	Reason for exclusion
Ahfmr 1997[4]	Incorrect study design - review
Bachoo 2009[11]	Incorrect study design - review
Brown 1992[37]	Comparator does not match protocol - other form of compression
Chant 1989[52]	Comparator does not match protocol - other form of compression
Chant 1985[54]	Comparator does not match protocol - other form of compression
Diehm 1996[81]	Incorrect outcomes reported
Geraghty 1989[102]	Probably the same study as Anderson 1990.
Jones 1980[125]	Comparator does not match protocol - other form of compression
Kakkar 1982[127]	Comparator does not match protocol - other form of compression
Labropoulos 1994[141]	Incorrect study design – laboratory study
Lippmann 1994[147]	Intervention does not match protocol - Unna’s boot
Michaels 2006[170]	Comparator does not match protocol – liquid sclerotherapy).
Mosti 2011[174]	Comparator does not match protocol- other form of compression
Murad 2011[178]	Incorrect study design – systematic review
Palfreyman 2009[200]	Incorrect study design – systematic review
Thaler 2001[260]	No relevant outcomes and does not match review question
Tisi 2011[269]	Incorrect study design – systematic review

J.4.2 Compression vs. interventional treatment

Table 104: Studies excluded from the clinical review

Ref ID	Reason for exclusion
Abramowitz 1973[3]	Intervention does not match protocol - liquid sclerotherapy only
Barwell 2004[13]	Population does not match protocol - treatment of chronic ulceration
Gohel 2007[105]	Population does not match protocol - treatment of chronic ulceration
Gohel 2005[104]	Population does not match protocol - treatment of chronic ulceration
Guest 2003[109]	Population does not match protocol - treatment of chronic ulceration
Leu 1993[144]	Intervention does not match protocol – foam sclerotherapy and compression applied concomitantly
Palfreyman 2009[200]	Incorrect study design - systematic review.
Schul 2011[240]	Population does not match protocol - CEAP1 only – not a true varicose veins population.
Shingler 2011[248]	Incorrect study design - systematic review.

J.5 Chapter 9 – interventional treatment

J.5.1 Stripping surgery vs. foam sclerotherapy

Table 105: Studies excluded from the clinical review

Reference	Reason for exclusion
Belcaro2003[16]	Intervention does not match protocol – avulsion
Belcaro2000[18].	Intervention does not match protocol – flush ligation and avulsion
Beresford1978[20]	Comparator does not match protocol – liquid sclerotherapy
Chant1972[53]	Comparator does not match protocol – liquid sclerotherapy
Doran1975[89]	Comparator does not match protocol – liquid sclerotherapy
Eifell2006[93].	Incorrect study design - study protocol .
Einarsson1993[94]	Comparator does not match protocol – liquid sclerotherapy
Haas2006[110].	Non English language publication
Hobbs1968[116]	Comparator does not match protocol – liquid sclerotherapy
Hobbs1974[117]	No relevant outcomes and does not match review question
Jakobsen1979[124]	Comparator does not match protocol – liquid sclerotherapy
Liamis2005[146].	Abstract only
Michaels2006A[169]	Comparator does not match protocol – liquid sclerotherapy
Miyazaki2005[171]	Incorrect study design - retrospective observational study and not an RCT.
Murad2011[178]	No relevant outcomes and does not match review questions
Neglen1993[94]	No relevant outcomes and does not match review questions
Rigby2004[228].	No relevant outcomes and does not match review questions
Rutgers1994[232]	Comparator does not match protocol – liquid sclerotherapy
VanDenBos2009[275].	Incorrect study design - systematic review .

J.5.2 Stripping surgery vs. endothermal ablation

Table 106: Studies excluded from the clinical review

Reference	Reason for exclusion
Anon2010[163]	Incorrect study design - systematic review
Basel2012[14]	Incorrect study design - probably non-randomised. Although stated in the abstract that this paper was randomised, there is no mention of randomisation in the paper itself. Instead, the methods section states that "the study was planned as a retrospective study".
Brar2010[33]	Incorrect study design - systematic review
Christenson2010[57]	Some patients with bilateral symptoms had each leg randomised to a different group, making QoL and pain results rather meaningless (as perception will be global not per leg).
Darwood2009[66]	Incorrect study design - systematic review
De Medeiros2005[71]	Intervention does not match protocol - laser group had high tie of SFJ – thus "non-standard" laser
De Medeiros2006[70]	Same study as de Medieros 2005, with identical outcomes
Disselhoff2008[85]	intervention does not match the protocol - cryostripping
Disselhoff2008[87]	intervention does not match the protocol - cryostripping

Reference	Reason for exclusion
Disselhoff2009[84]	Comparator does not match protocol - cryostripping instead of standard stripping
Disselhoff2011[86]	intervention does not match the protocol - cryostripping
Kalteis2008[130]	Intervention does not match protocol - laser was combined with SFJ ligation – thus “non standard” laser
Kundu2011[140]	Incorrect study design - systematic review
Luebke2008[149]	Incorrect study design - systematic review
Nesbitt2011[184]	Incorrect study design - systematic review
Subramonia2010[257]	Economic analysis and otherwise same study as Subramonia 2010B
Tellings2011[259]	Incorrect study design - systematic review
Theivacumar2009[261]	Incorrect study design - cohort study
Vuylsteke2006[279]	Incorrect study design - not randomised
Xenos2009[287]	Incorrect study design - systematic review

J.5.3 Foam sclerotherapy vs. endothermal ablation

Table 107: Studies excluded from the clinical review

Reference	Reason for exclusion
King2009[135]	Endovenous ablation and sclerotherapy applied concomitantly – not a comparison.
Koroglu2011[137]	Endovenous ablation and sclerotherapy applied concomitantly – not a comparison.
Luebke2008[150]	Incorrect study design - systematic review

J.5.4 Tributary treatment: avulsion vs. foam sclerotherapy

Table 108: Studies excluded from the clinical review

Reference	Reason for exclusion
Belcaro 2000[18]	Intervention does not match protocol - did not include avulsion surgery
Belcaro 2003[16]	Unclear if the foam sclerotherapy was a tributary treatment.
Belcaro 2003B[15]	Identical report to the included Belcaro 2003 study.
Brethauer 2001[35]	Comparator does not match protocol - liquid sclerotherapy
De Roos 2003[73]	Comparator does not match protocol - liquid sclerotherapy

J.5.5 Truncal and tributary treatment vs. truncal treatment alone

Table 109: Studies excluded from the clinical review

Ref ID	Reason for exclusion
Belcaro 1998[17]	Non English speaking publication
Belcaro 2000[18]	Intervention does not match protocol - liquid sclerotherapy
Belcaro 2003B[15]	Foam sclerotherapy was done up to 6 months after the surgery
Kim[132]	Comparator does not match protocol - included tributary treatments given with endovenous ablation.
King 2009[135]	Incorrect study design - no comparator
Koroglu [137]	Did not address the review question.
Mekako 2006[165]	Incorrect study design - no comparator
Merchant 2005[168]	No relevant outcomes and does not match review question
Nicolini 2005[188]	Intervention does not match protocol - those receiving tributary treatments included those receiving such treatments during the follow-up period (i.e. not just those who had tributary treatments at the same time as the truncal treatment)
Sadick 2007[233]	Incorrect study design - no comparator
Schanzer 2010[238]	Study comparator does not match protocol
Theivacumar 2006[264]	Abstract only
Theivacumar 2007[265]	Contained information that 40% of patients undergoing laser ablation to GSV required delayed tributary treatment. However this paper did not address the review question.
Theivacumar 2008[266]	No relevant outcomes and does not match review question
Theivacumar 2008A [267]	This study had one group where sclerotherapy was used concomitantly with EVLA, but this was not to treat tributaries (it was to treat below knee truncal reflux).
Theivacumar 2009[261]	No relevant outcomes and does not match review question
Theivacumar 2009A[263]	No relevant outcomes and does not match review question
Theivacumar 2009B[262]	Contained information that 44% of patients undergoing laser ablation to GSV required delayed tributary treatment. However this paper did not address the review question.
Welch 2006[283]	No relevant outcomes and does not match review question
Weiss RA, Weiss MA.[282]	No relevant outcomes and does not match review question

J.6 Chapter 10 – compression after interventional treatment

Table 110: Studies excluded from the clinical review

Reference	Reason for exclusion
Biswas 2007[23]	Compared different durations of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Bond 1999[29]	Compared different types of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
de Roos 2008[72]	Incorrect study design - no comparator
De Jode 1970[75]	Intervention does not match protocol - liquid sclerotherapy used
Din 1992[83]	Intervention does not match protocol - liquid sclerotherapy used
Fraser 1985[73,100]	Intervention does not match protocol - liquid sclerotherapy used
Lugli 2009[151]	Compared different forms of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Mariani 2011[159]	Compared different forms of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Melrose 1979[166]	No relevant outcomes and does not match review question
Mosti 2009[173]	Compared different levels of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
O'Hare 2010[190]	Compared different durations of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Raraty 1999[218]	Compared different durations of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Rhodes 1972[227]	Intervention does not match protocol - liquid sclerotherapy used
Rodrigus 1991[231]	Compared different durations of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Shingler 2011[248]	Incorrect study design - systematic review
Shouler 1989[249]	Compared different levels of compression; this would have met the inclusion criteria for part b) of the research question if part a) had shown a reasonable level of efficacy for compression as an adjuvant therapy.
Travers[270]	No relevant outcomes and does not match review question
Tretbar 1970[272]	Intervention does not match protocol - liquid sclerotherapy used
Weiss 1999A[281]	Intervention does not match protocol - liquid sclerotherapy used

Appendix K: Excluded economic studies

K.1 Chapter 8 – conservative management

K.1.1 Compression vs. interventional treatment

Table 111: Studies excluded from the economic review

Reference	Reason for exclusion
Eskelinen et al. 2009[96]	Economic analysis is based on a cohort study and it is unclear whether the QALYs reported are correct. It is unclear whether the 15-dimension quality-of-life instrument has been validated.

K.1 Chapter 9 – interventional treatment

K.1.1 Stripping surgery vs. foam sclerotherapy

Table 112: Studies excluded from the economic review

Reference	Reason for exclusion
Beresford et al 1978[20]	Dated article
Bountouroglou et al 2006[30]	This study did not report QALYs. More applicable evidence was available for this comparison.
Piachaud & Weddell 1972[207]	Dated article
Piachaud & Weddell 1972A[206]	Dated article
ZonMw 2005 [185]	Study results are not published. It is stated that a full report is available from the authors. Attempts to make contact with the authors, however, failed.

K.1.2 Stripping surgery vs. endothermal ablations

Table 113: Studies excluded from the economic review

Reference	Reason for exclusion
Disselhoff et al 2009[84]	The study is an economic analysis carried out alongside a randomized controlled comparing cryostripping with endovenous laser ablation.
Eidson et al 2011[92]	This is a retrospective cohort study comparing the relevant treatments over a 6 month period.
Medical Advisory Secretariat 2010[163]	This is a costing and budget impact study to identify resource and cost differences between the two interventions compared.
Ontario Health Technology Advisory Committee[1]	This is a costing and budget impact study to identify resource and cost differences between the two interventions compared.
Rasmussen et al 2007[219]	This study was excluded as more recent results are reported in Rasmussen et al. 2011 [221].
Rasmussen et al 2011[219]	This study was based on the Danish healthcare system and does not report QALYs. It has a lower applicability than other evidence for this comparison.
Rautio et al 2002[224]	This study was based on the Finish healthcare system and does not report

Reference	Reason for exclusion
	QALYs. It has a lower applicability than other evidence for this comparison.
Solis et al 2009[252]	Actual cost estimates are not provided but rather symbols are used to indicate that endovenous laser ablation is more expensive than stripping surgery.
Subramonia and Lees 2010[257]	This study does not report QALYs. It has a lower applicability than other evidence for this comparison
Vuylsteke et al 2006[279]	This study was based on the Belgian healthcare system and does not report QALYs. It has a lower applicability than other evidence for this comparison.

K.1.3 Foam sclerotherapy vs. endothermal ablation

Table 114: Studies excluded from the economic review

Reference	Reason for exclusion
Rasmussen et al 2011[221]	This study was based on the Danish healthcare system and does not report QALYs. It has a lower applicability than other evidence for this comparison.

Appendix L: Cost-effectiveness analysis of interventional treatments and conservative care

L.1 Introduction

Interventional treatments for varicose veins (surgery, foam sclerotherapy and endothermal ablation techniques) are likely to have significant resource implications, and as such it is important to identify which of these treatments represents a cost-effective use of NHS resource. Two published UK economic evaluations were identified in this area[106,170]Michaels and colleagues (2006) compared surgery, liquid sclerotherapy and conservative care in various groups with differing stages of disease and found surgery to be the most cost-effective option. However this analysis did not look at endothermal techniques or foam sclerotherapy, and is therefore not complete for our purposes. The second evaluation, Gohel and colleagues (2010), was subject to several limitations; in particular, the costs were not thought to be representative of common practice as they were based on modified reference costs, and the authors appear to assume that recurrence rates do not differ after different modalities of treatment. The conclusions of the model must therefore be interpreted with caution, and are of limited value in informing recommendations.

We are also aware of an on-going NHS Health Technology Assessment (HTA) project to investigate the cost effectiveness of minimally invasive techniques.[239] There is overlap between the HTA project and the analysis presented here, however we are aware of a few key differences: in contrast to our model, the aforementioned project does not include conservative care as a comparator, the clinical outcomes included in the network meta-analysis (NMA) are different, and as such the model is based on different clinical data. The HTA project is still being revised, therefore no further comment can be made here. Overall, the GDG did not deem the existing literature to be sufficient on which to base recommendations. Interventional treatments were therefore identified as a priority for original economic analysis.

Initially it was planned that analyses would also look at the cost-effectiveness of these treatments at different stages of the disease, thereby addressing the question of the optimal timing of intervention. However, a lack of relevant data meant this was not possible. This analysis therefore focuses on the cost effectiveness of the various interventional treatments for varicose veins, in comparison to non-invasive conservative care, in the general primary varicose veins population.

Analysis of patients with bilateral disease was carried out separately as a cost-comparison, with the results and their implications discussed thoroughly by the GDG.

L.2 Methods

L.2.1 Model overview

A cost-utility analysis was undertaken where costs were considered from a UK NHS and personal social services perspective and health outcomes expressed as quality adjusted life years (QALYs). Costs and QALYs were both discounted at 3.5% per annum, in accordance with the NICE reference case[182].

L.2.1.1 Comparators

Four treatments were considered in the base case:

- Surgery (stripping and ligation) – with or without tributary treatment, carried out as a day case procedure under general anaesthetic
- Endothermal techniques (RFA & EVLA) with concurrent phlebectomy – carried out as an outpatient procedure under local anaesthetic
- Foam sclerotherapy – with or without tributary treatment, carried out as an outpatient procedure under local anaesthetic
- Conservative care (compression therapy)

Endothermal techniques without concurrent phlebectomy were evaluated as a sensitivity analysis.

L.2.1.2 Population

Adults with primary unilateral great saphenous vein (GSV) incompetence, who are potentially suitable for treatment by any of the four treatment options.

In some cases, particular treatments may not be suited to an individual patient. Decision models are designed to identify the optimal choice between two or more alternative strategies; the choice between the comparators only applies to people for whom all of these are a possibility.

Sensitivity analyses included unilateral patients receiving concurrent treatment of the small saphenous vein (SSV), and a cost comparison to inform GDG discussion around treatment of patients with bilateral varicose veins.

L.2.1.3 Time horizon

The time horizon of the model was five years in the base case. This was chosen as the appropriate horizon as there is no differential mortality effect between treatment options, and no reliable evidence was found to document differences in costs and health related quality of life past this time horizon. Extrapolation of follow-up data (data is limited to a 3 year follow-up) past the 5 year time horizon would have been subject to a great deal of uncertainty and was not deemed to be appropriate in this instance.

Sensitivity analyses included evaluation over a 3 year time horizon, in line with the maximum follow-up time of the clinical data.

L.2.2 Approach to modelling

Interventional treatments for varicose veins are used to occlude, obliterate or strip varicose veins, thereby reducing patient symptoms and improving quality of life. When these outcomes are not achieved, top-up treatment can be given to supplement the initial treatment. For the purpose of the model, this combination of initial treatment and top-up treatment was considered to be one treatment episode. All patients in the model have an initial treatment episode (either outpatient or day case depending on the treatment option), with different treatments leading to different proportions of individuals requiring top-up treatment, resulting in a difference in costs and QALYs associated with the initial treatment episode.

Patients in the model experience an increase in quality of life (QoL) once the initial treatment episode is complete. The difference in QALYs was driven by the length of time this increase in QoL was sustained for, before a patient experienced recurrent varicose veins. The probability of having recurrent varicose veins differed by treatment and for the purpose of the model was taken from a network meta-analysis described in section L.2.3.2.2 below. The NMA was based on clinical recurrence data, which was used to capture the development of symptoms of varicose veins in a treated limb. Clinical recurrence was chosen over other possible definitions of recurrence because symptoms (as opposed to reflux, recanalisation, or any other definition) have a direct impact on QoL. Patients could undergo a second treatment episode in the model, to alleviate symptoms of recurrent varicose veins and improve QoL again. Further information and technical details are given in the subsequent sections.

L.2.2.1 Key definitions

A **treatment episode** consists of a treatment for every patient, and a top-up treatment for the proportion of individuals who require it. There is potential for two treatment episodes in the model; an **initial treatment episode** which all patients in the model receive, and a **second treatment episode** which is given to a proportion of individuals following clinical recurrence. The second treatment episode is distinct from top-up treatment, which is considered to be part of a treatment episode.

Top-up treatment is given as part of a treatment episode (within 2 months of the initial treatment) if treatment is not deemed to be complete (i.e. if the vein undergoing treatment has not been occluded or obliterated, or if additional treatment of residual varicosities is needed). Top-up treatment was assumed to always be foam (see Table 115). In some cases the need for top-up treatment could be identified by a follow-up appointment if one is given, or the top-up treatment could have been planned before the initial treatment; in other cases, the patient may present with a need for top-up treatment. The inclusion of top-up treatment in the model is not intended to imply a recommendation of routine follow-up appointments. The concept of top-up treatment is adapted from the aforementioned HTA project,[239] in which it is used to refer to residual varicose veins, and does not include unsuccessful occlusion.

Clinical recurrence is defined as development of symptoms of varicose veins in a treated limb. For the purpose of the network meta-analysis, papers which report clinical recurrence as an outcome were taken at face value.

L.2.2.2 Model structure

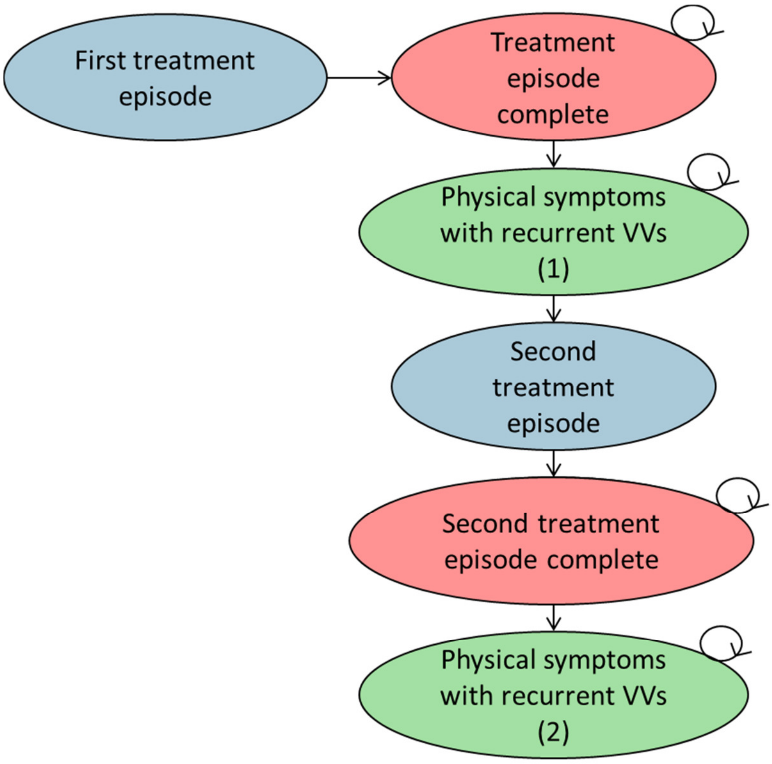
A Markov model was constructed to calculate costs and QALYs for each comparator; the key health states and transitions can be seen in Figure 159. The simplified diagram does not show death, but patients could die of all-cause mortality at any point during the model's five year time horizon.

Patients enter the model through the 'First treatment episode' state. Following completion of the treatment episode, patients move to a state of 'treatment episode complete', where they do not require any further treatment. They remain in this state until they experience clinical recurrence, at which point they transition to the state 'Physical symptoms with recurrent VVs (1)'. Patients cannot experience clinical recurrence in the first three cycles post treatment, to allow time for all top-up treatments to take place.

Only a proportion of patients with clinical recurrence go on to have further interventional treatment, whilst the rest receive conservative care. For those who do receive further interventional treatment, a delay of 6 months is assumed between the onset of clinical recurrence and the second treatment episode. This delay is based on clinical opinion and captured in the model through a series of tunnel states (these states are omitted from Figure 159 for simplicity). Following the second treatment episode, a patient can experience clinical recurrence again, but will not receive further treatment; instead they remain in the state of 'physical symptoms with recurrence VVs (2)' and receive conservative care. Conservative care received at this point is assumed not have an impact on QoL

Conservative care was modelled separately to the other three interventions, as the outcomes of completed treatment and clinical recurrence are not clinically meaningful when considering this management technique. Instead, the difference in quality of life between patients undergoing surgery and conservative care (as reported in Michaels2006[170]) was used to calculate the difference in QALYs over time between these two treatments. This information was then used to calculate the QALYs expected from conservative care, relative to the QALYs computed by the model for surgery. Costs were calculated by applying an annual cost to all those individuals in the model and receiving conservative care.

Figure 159: Model diagram



Schematic diagram of the Markov model designed to compare the cost-effectiveness of treatments for varicose veins. The Markov modelling approach involves a transition between different health states over time. The model is divided into monthly cycles. At the end of each cycle a transition to another health state is possible, unless people enter into an 'absorbing state' from which they cannot transition. In this model, the absorbing state is 'Physical symptoms with recurrent VVs (2)'.

The model was built with a one month cycle length as this was deemed to be the minimum clinically meaningful time interval to detect differences between interventions. All the probabilities, costs and health utilities were converted to reflect the one-month cycle length.

L.2.2.3 Key assumptions

The model employed the following key assumptions:

Table 115: Key assumptions

Assumption	Comment
Rates of top-up treatment are the same in the initial and second treatment episode (ie after retreatment)	The GDG deemed this to be a reasonable assumption
Top-up treatment is always foam sclerotherapy	As the modality of top-up treatment does not affect the rate of recurrence (see assumption below), this will only effect the cost of top-up treatment. The GDG deemed this to be a reasonable simplifying assumption.

Assumption	Comment
Patients who have had top-up treatment have the same probability of recurrence as those who haven't had top-up	The GDG deemed this to be a reasonable simplifying assumption
Constant hazard of recurrence	This was deemed to be a reasonable simplifying assumption as the time horizon of the model is relatively short
There is a 6 month delay between the onset of clinical recurrence and the second treatment episode	This is included to reflect the time between the onset of symptoms and subsequent interventional treatment.
A patient can only receive two treatment episodes in total	This is a simplifying assumption for the model but is expected to be a fair reflection of routine clinical practice
Proportions of patients having each modality of second treatment is independent of the modality of their initial treatment	The method of retreatment is more likely to be based on individual patient characteristics and the nature of the recurrence, rather than the modality of initial treatment. As the model cannot capture these factors for individual patients, the GDG deemed this to be a reasonable assumption.

L.2.2.4 Uncertainty

The model was built probabilistically to take account of the uncertainty surrounding each input parameter. In order to characterise uncertainty, a probability distribution was defined for each parameter based on error estimates from the data sources (e.g. standard errors or confidence intervals). The way in which distributions are defined reflects the nature of the data (see Table 116). When the model was run, a value for each input was randomly selected from its respective distribution. The model was run repeatedly (10, 000 times) to obtain mean cost and QALY values.

Various sensitivity analyses were also undertaken to test the robustness of model assumptions and data sources. In these analyses, one or more inputs were changed and the analysis was rerun in order to evaluate the impact of these changes on the results of the model.

Table 116: Distributions used in probabilistic cost-utility analysis

Parameter	Type of distribution	Properties of distribution
Cost	Gamma	Bounded at 0, positively skewed. Derived from mean and standard error
Pre-treatment utility	Beta	Bounded on 0 – 1 interval. Derived from mean and sample size
Utility improvements and decrements	Lognormal	Bounded at 0. Derived from log of mean utility change and standard error of log of utility change
Utility difference between conservative care and surgery	Normal	Derived from mean and variance
Baseline risk and relative effects	Distribution estimated by sampling from network meta-analysis output	

L.2.3 Model Inputs

L.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. All inputs were checked for face validity by the clinical members of the GDG. A summary of the model inputs used in the base-case analysis is provided in Table 117 Table 118 below. More details on sources, calculations and rationale for selection can be found in subsequent sections.

Table 117: Summary of base-case model inputs and cohort settings

	Input	Source
Comparators	Surgery, foam sclerotherapy, endothermal with phlebectomies, conservative care	GDG consensus
Population	Adults with primary unilateral GSV incompetence	GDG consensus
Initial cohort settings	Age: 50 Female: 65%	Weighted average across relevant RCTs[1]
Perspective	NHS and PSS	NICE reference case[182]
Time horizon	5 years	GDG consensus
Discount rate	Costs: 3.5% QALYs: 3.5%	NICE reference case[182]

GSV = great saphenous vein

[1] the RCTs included in the network meta-analysis for clinical recurrence

Initial cohort settings

A starting age of 50 was used in the model to represent the average age of people undergoing treatment for varicose veins, and the cohort was assumed to be 65% female, based on the characteristics of patients in the included RCTs. These cohort characteristics were validated against HES data[121] which confirms that the average age of patients undergoing day case treatment for varicose veins is approximately 50, and that roughly two thirds of these patients are female.

Table 118: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Utility weights				
Primary varicose veins	0.764	Beta	$\alpha = 37600, \beta = 12800$	PROMs[119]
Change in utility (from baseline) post treatment	+0.091	Lognormal	$\mu = -2.397, \sigma = 0.0007$	PROMs[119]
Change in utility (from baseline) due to recurrent varicose veins	-0.093	Lognormal	$\mu = -2.206, \sigma = 0.0128$	Beresford 2003[21]
Conservative care (relative to surgery at 1 year)	-0.101	Normal	$\mu = 0.0004, \sigma = 0.0198$	Michaels 2006[170]
Transition probabilities				
Probability of requiring top-up treatment (within 2 months post treatment)				
Surgery	5%	Deterministic SA only		GDG estimate
Endothermal	5%	Deterministic SA only		GDG estimate
Foam Sclerotherapy	20%	Deterministic SA only		GDG estimate
Conservative care	NA			
Probability of recurrence (per month)				
Surgery	0.008331	Point estimate and uncertainty from NMA		
Endothermal	0.005833	Point estimate and uncertainty from NMA		
Foam Sclerotherapy	0.009141	Point estimate and uncertainty from NMA		

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Conservative care	NA			
Cost (£)				
Surgery	£908	Gamma	See Table 126	See Table 126
Endothermal	£624	Gamma	See Table 128	See Table 128
Foam Sclerotherapy	£315	Gamma	See Table 129	See Table 129
Conservative care[a]	£234	Deterministic SA only		
Additional cost associated with retreatment	£417	Gamma	See Table 131	See Table 131

SA = Sensitivity analysis; NMA=network meta-analysis

[a]*this is an annual cost (first year incurs and additional £15)*

L.2.3.2 Baseline event rates and relative treatment effects

L.2.3.2.1 Top-up treatment rates

Limited data on treatment failure was available from the randomised trials, often based on different definitions of failure and very short follow-up of just a few days. In addition, treatment failure, however defined, is not the only reason that top-up treatment may be undertaken. For example, further treatment could be necessary to eradicate residual varicosities which were not treated initially (this may or may not have been planned at the time of the initial treatment). The data on treatment failure from the trials was therefore not considered to be relevant to the need for top-up treatment as defined in our model. For this reason, the proportions of patients requiring top-up after each treatment are based on GDG estimate (see Table 118).

L.2.3.2.2 Clinical recurrence

The results of conventional meta-analyses of direct evidence alone make it difficult to determine which intervention is the most effective treatment. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not fully inform the choice between all the possible treatments, and having a series of discrete pair wise comparisons can be disjointed and difficult to interpret
- There are overlapping comparisons that could potentially give inconsistent estimates of effect.

This is particularly problematic for probabilistic analysis. To overcome these problems, a Bayesian network meta-analysis (NMA)[40] was conducted in WinBUGS.

Conventional meta-analysis assumes that, for a fixed-effect analysis, the relative effect of one treatment compared to another is the same across an entire set of trials. In a random-effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same relative effect across all trials of intervention A compared to intervention B as it does across trials of intervention A versus intervention C, and so on. Thus, in a random-effects network meta-analysis, the assumption is that intervention A has the same effect distribution across all trials of A versus B, A versus C and so on.

The aim of the NMA was to calculate treatment-specific probabilities of clinical recurrence following each of the different treatments. Clinical recurrence was chosen over other possible definitions of recurrence because symptoms (as opposed to reflux, recanalisation, or any other definition) are most likely to have an impact on QoL. The GDG did not think it was appropriate to combine different measures of recurrence into one measure of effect. The definition of clinical recurrence as used in this analysis was given in section L.2.2.1.

Statistical analysis

When modelling an outcome such as clinical recurrence, it is important to consider the different follow-up times of the various trials, as longer follow-up is likely to result in more reported recurrences. To account for this, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a complementary log-log (cloglog) link function used to model the event rate. The following logic was used to calculate hazards and hazard ratios:

Let BH and HR denote the baseline hazard (from the surgery arms) and treatment-specific hazard ratio for clinical recurrence; let θ represent the cloglog of the probability of recurrence, p, and let $time$ represent the duration of follow-up. Then:

$$\theta = Ln\,(time) + \ Ln\,(HR) + \ Ln\,(BH)$$

And:

$$p = 1 - \exp\{-\exp\theta\}$$

Surgery was chosen as the baseline comparator as it featured in the most trials. The baseline hazard was estimated on the clog-log scale through a meta-analysis of the surgery arms of the included trials. The resulting predictive distribution was inputted to the NMA for adjustment by the treatment specific hazard ratios to calculate the probability of clinical recurrence for each treatment. The codes for both the baseline and relative effects models were adapted from that provided on the NICE decision support unit website, and run in WinBUGS 14.

The baseline and relative effects models were run for 50,000 iterations with burn in periods of 50,000. Vague uninformative priors were combined with the data-driven likelihood functions to produce posterior probability estimates. Convergence was assessed by examining the history and kernel density plots.

Fixed and random effects NMAs were run, and goodness of fit estimated by calculating the total residual deviance and deviance information criteria (DIC) for each of the models. A total residual deviance close to the number of unconstrained data points (the number of trial arms in the analysis) indicated a model explaining the data at a satisfactory level. The DIC provides a measure of goodness of fit which penalises model complexity,[79] which is useful for comparing models. The choice of a fixed or random effects model can therefore be made by comparing their goodness-of-fit to the data.

Network and Data

A total of eight studies included in the clinical reviews of the relevant treatments included clinical recurrence as an outcome. The trials included a variety of patients at differing levels of severity of varicose veins, further information on the trials can be found in chapters X and X of the full guideline. Surgery featured in all eight of the trials, endothermal treatment featured in seven, and foam sclerotherapy in two. One trial included all three comparators. The network of trials compared in the NMA is shown in Figure 160 and the included data in

Table 119. In

Figure 160 the number of trials included for each pair-wise comparison is noted in parentheses.

Note that the comparison between sclerotherapy and endothermal treatment includes only one trial. This single included study is a three arm trial which includes all of our comparators. Three arm trials are internally consistent, and as such there is no potential for inconsistency within our network, only for between-trial heterogeneity. This is discussed further by Dias and colleagues in technical support document 4,[80] in which the authors explain that 'loops of evidence that are potentially inconsistent can only arise from structures in which there are three distinct trials or sets of trials'.

Figure 160: Network of trials compared in the network meta-analysis

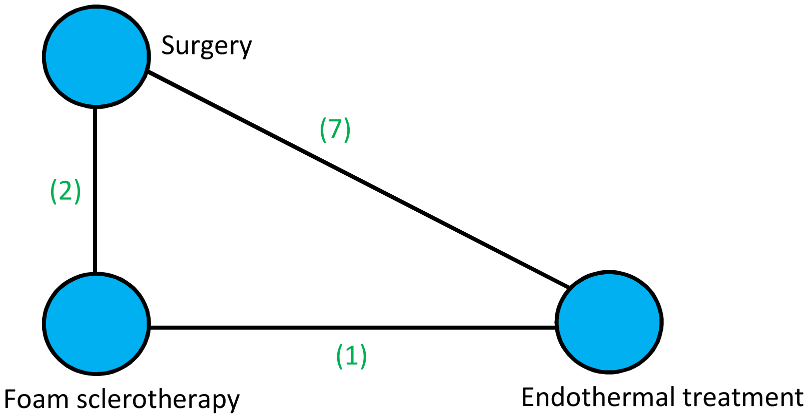


Table 119: Clinical recurrence trial data for network meta-analysis

Study name	Follow up time (months)	Clinical recurrence			Total number of patients			Treatments compared		
		Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
Shadid 2012[244]	24	16	24	-	177	213	-	S	FS	-
Rasmussen 2011[221]	12	16	17	23	108	123	245	S	FS	E
Carradice 2011[46]	12	23	5	-	113	124	-	S	E	-
El Kaffas 2011[113]	24	9	12	-	90	88	-	S	E	-
Perala 2010[204]	36	2	5	-	13	15	-	S	E	-
Pronk 2010[213]	12	3	3	-	56	49	-	S	E	-
Rasmussen 2010[220]	24	25	18	-	68	69	-	S	E	-
Rass 2011[222]	24	33	28	-	143	173	-	S	E	-

Abbreviations: S = surgery; E = endothermal treatment; FS = foam sclerotherapy

Network meta-analysis results

The total residual deviance was 25.3 for the fixed effects model and 18.6 for the random effects model which, when compared to 17 unconstrained data points, shows that the random effects model fitted the data reasonably well. DIC statistics of 105.5 and 103.4 were calculated for the fixed effects and random effects models respectively which, although the difference is small, suggests that the random effects model is the preferred option. Results are therefore presented for the random effects model only.

The final treatment-specific probability estimates and their associated confidence intervals can be seen in Table 7.

Table 120: Network meta-analysis results – probability of clinical recurrence

Treatment	Clinical recurrence (probability per month)			
	Mean	Standard deviation	Median	Credible interval
Surgery	0.008818	0.00306	0.008331	0.004284 - 0.0161
Endothermal treatment	0.006532	0.003448	0.005833	0.002424 – 0.01472
Foam sclerotherapy	0.01115	0.009929	0.009141	0.002795 – 0.03093

As shown in Table 121, endothermal treatment was associated with the lowest probability of recurrence per month. These estimates were used to parameterise treatment effects in the decision model; deterministic point estimates were based on median values, with PSA values sampled from the WinBUGs CODA output.

A posterior estimate of heterogeneity - the between trial standard deviation - was found to be 0.58. An estimate of this magnitude indicates a large amount of variation in treatment effects calculated from different trials.

L.2.3.2.3 Retreatment

Not all patients are retreated after experiencing clinical recurrence; for some patients this is because they do not wish undergo further treatment, whereas for others it is because they are not deemed suitable for further treatment. The GDG estimated that 75% of patients would receive further interventional treatment, and it was assumed that the remaining 25% would receive conservative care. This estimate was subject to wide ranging deterministic sensitivity analysis.

For those individuals who do undergo a second treatment episode, the mode of treatment is likely to depend on the nature of their recurrence, alongside further patient characteristics. The GDG estimated that the following proportions of patients would have each type of retreatment (Table 121).

Table 121: Method of retreatment

Second treatment	% patients receiving each method of retreatment
Surgery	12%
Foam sclerotherapy	42%
Endothermal techniques	46%

These proportions represent an average over the 5 year time horizon, and were the same irrespective of the modality of the initial treatment. There is substantial uncertainty surrounding these estimates, however due to the nature of the model they are unlikely to drive the results. Nevertheless, these proportions were subject to extensive deterministic sensitivity analysis (see section 0).

L.2.3.2.4 Adverse events

Evidence on adverse events due to treatment identified by the clinical review was weak; different trials report different outcomes, and measure them in different ways. For example, pain is measured by VCSS at 1, 2 and 6 months in Figueiredo 2009,[97], as a dichotomous outcome at one year in Pronk 2011,[213] and by SF-36 in Rasmussen 2011.[221] In addition, the GDG members felt that the adverse event profiles of the different treatments were similar to the extent that their inclusion would not benefit the model; therefore adverse events were not included in the analysis.

Whilst factors such as time to return from work, and time to return to usual activities may differ between treatments, these do not fall within the model’s perspective of the NHS and PSS, and are therefore outside the remit of this analysis.

L.2.3.2.5 Mortality

The treatments considered in the analysis are not assumed to have any differential effect on mortality, yet patients can die at any point in the model. Age-specific all-cause mortality, weighted for the gender split of the cohort population, was based on the most recent available life tables for England and Wales (2008-20010).[191]

L.2.3.3 Utilities

In cost-utility analyses, measures of health benefit are valued in terms of quality adjusted life years (QALYs). The QALY is a measure of a person's length of life weighted by a valuation of their health related quality of life (QoL) over that period. The weight used is called a utility value, which is a measurement of the preference for a particular health state, with a score ranging from 0 (death) to 1 (perfect health). Questionnaires such as the SF-36 and SF-12 provide generic methods of describing QoL, while the EQ-5D, HUI, and SF-6D also include preference-based valuations of each health state, allowing calculation of utility scores.

The preferred method for determining utilities for NICE economic evaluations is the EuroQoL (EQ-5D) questionnaire[182]. The EQ-5D comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. For the NICE reference case, preferences from the general public should be used. In keeping with this preference, EQ-5D data was collected from the RCTs included in the clinical review. Only four studies provided EQ-5D data, all of which are shown in Table 122. Studies which reported SF-36 data or disease specific quality of life measures (such as the AVVQ or CIVIQ2) without EQ-5D are not included here.

Table 122: EQ-5D data from clinical trials

Study	Relevant comparators	Utility values				
		Baseline	3 months	6 months	12 months	24 months
Carradice 2009[461]	EVLA + phlebectomy	0.81 (0.79-1.0) [2]	1.0	NR	1.0 (1.0 – 1.0)[2]	NR
	EVLA without phlebectomy	0.83 (0.75 – 1.0) [2]	0.82	NR	1.0 (0.89 – 1.0)[2]	NR
Carradice 2011[48]	Surgery	0.84 (0.8 – 1.0) [2]	NR	NR	1.0 (0.84 – 1.0)[2]	NR
	EVLA	0.85 (0.8 – 1.0) [2]	NR	NR	1.0 (0.87 – 1.0)[2]	NR
Michaels 2006[170](Group 3 only: severe varicose veins)	Surgery	0.76 (0.19)	NR	0.89 (0.13)	0.87 (0.14)	0.84 (0.21)
	Conservative care	0.77 (0.18)	NR	0.80 (0.17)	0.78 (0.18)	0.85 (0.17)
Shadid 2012[244]	Surgery	Change from baseline at 2 years: +0.064 (NR)				
	Foam sclerotherapy	Change from baseline at 2 years: +0.061 (NR)				

Abbreviations: NR = not reported

Values are mean (SD) EQ-5D scores unless otherwise stated

[1] Mean utility values estimated from low resolution graph. Graph also reports data at 1 week and 6 week follow-up

[2] median (interquartile range)

EQ-5D is not consistently reported in the trials. It is clear from Table 122 that this outcome is reported at different follow-up times for the different comparators, thus the evidence does not lend itself to an accurate comparison of the quality of life after each treatment individually. A search of the economic and quality of life literature was therefore carried out to supplement the EQ-5D data found in the trials. The search identified two economic analyses which included EQ-5D data[106,170]: Gohel and colleagues employed the baseline and post treatment EQ-5D scores from the surgery arm in Michaels, and the modelling section of Michaels used a combination of SF-6D and EQ-5D from the same trial. Two additional economic evaluations[84,223] were found which used utility data calculated from the SF-6D. None of these economic analyses were considered beneficial in informing utility inputs for our model.

The search also identified two further randomised trials which included EQ-5D data.[90,189] Neither of these studies were included in the clinical review for this guideline because the treatments compared in these trials were not relevant to the clinical questions included in this guideline. These studies were therefore not considered to be useful in informing inputs for the model.

An additional source of utility data is the Patient Reported Outcome Measures (PROMs), collated by the Department of Health (DH). Since 2009, the DH has required providers of varicose veins surgeries in England to collect and report PROMs. In practice, this means that all providers of NHS-funded varicose vein surgeries are expected to invite patients to complete a pre-operative questionnaire. Post-operative questionnaires are then sent to patients at least 3 months following their operation. The questionnaires completed by the patient, record self-reported health status assessed through a mixture of generic (EQ-5D and EQ-VAS) and condition-specific (AVVQ) questions. Where EQ-5D data is collected, this can be used to calculate the mean pre- and post-treatment utility scores of individuals receiving these treatments across England.

As of October 2012, finalised data are available for April 2010- March 2011. 8,624 records are available from varicose veins patients with valid EQ-5D responses in both pre- and post-operative questionnaires.[120] The mean utility score pre- and post-treatment, is available on the HES website, however this data does not specify results by varicose veins procedure. In theory, a dataset can be purchased from the Department of Health which would allow the data to be analysed by varicose veins procedure. However, given the likely population biases and computational time associated with analysis of such a large, incomplete data set, it was not thought that the benefits of purchasing this data set would justify the cost.

The PROMs data available from the HES website[119] is documented in Table 123.

Table 123: PROMs data

	Mean EQ-5D	SD	Number of completed questionnaires
Baseline	0.746	0.234	14533
Health gain post treatment	+0.096	0.256	8624[1]

[1] *all valid post-operative questionnaires, for which there is a valid pre-operative questionnaire*

Neither the data from the clinical review, nor the PROMs data provide reliable differential figures on the increase in utility following the different types of treatment. Therefore in the model patients receive the same increase in utility after treatment, regardless of treatment type. The PROMs data was used in preference to the clinical trial data in the model, as it reflects the mean change in utility for individuals undergoing treatment for varicose veins in routine clinical practice.

The baseline value was used in the model to represent the utility of a patient with primary varicose veins, i.e. when a patient first receives treatment. As PROMs data is measured at a minimum of 3 months after treatment, the health gain was applied 3 months after completed treatment (either initial or secondary). The increase in utility over the 3 months immediately after treatment was assumed to be linear, and was applied in the model through a series of tunnel states until the 3 month post utility value was achieved. For the probabilistic analysis, the baseline value was modelled with a Beta distribution, and the health gain was modelled with a Lognormal distribution, as specified in Table 118.

Utility decrement associated with recurrent varicose veins

We conducted a search to investigate whether recurrent varicose veins were associated with a different level of QoL to primary varicose veins. Two studies[21,198] were identified in this area, although neither reported utility values. One study mentioned SF36 data but was only available in abstract form,[198] and the other reported SF-36 data.[21] Both of these papers were co-authored by GDG members, who we approached for further information, yet unfortunately no further data was available.

In 2008, Ara and Brazier published a method of predicting mean EQ-5D preference based index score using published mean cohort statistics from the eight dimensions of the SF-36 health profile.[9] Therefore, in the absence of any utility data, we mapped the SF-36 data from Beresford 2003[21] to the EQ-5D. In order to use the mapping algorithms, values for each of the eight dimensions of the questionnaire are required. These values were only reported in graphical format, and were therefore estimated using Grab it!, a programme which can be used to digitise graphs. The estimation was made 3 times, and a mean value taken. The resulting values for each of the SF-36 domains are documented in Table 124.

Ara and Brazier present several different equations to predict EQ-5D from SF-36, the choice of which depends on the outcome to be mapped. Ara and Brazier state 'when comparing incremental differences between study arms or changes over time, Equation 4 is the preferred choice'; the outcome of interest here was the difference between the utility of people with primary and recurrent varicose veins, thus Equation 4 was chosen. No measure of uncertainty was provided in the graph, so the mapping algorithm was applied deterministically. The results of the mapping exercise, including the difference in utility between individuals with primary and recurrent varicose veins, are provided in Table 124. In the model, the utility of individuals with recurrent varicose veins was calculated by subtracting the difference from the primary varicose veins utility weight, and was modelled probabilistically using a Lognormal distribution (Table 118).

Table 124: SF-36 and EQ-5D data for primary and recurrent varicose veins

	PF	SF	RP	RE	MH	VT	BP	GH	EQ-5D	Difference
Primary	82.1	87.1	78.8	87.4	77.5	64.0	71.7	74.8	0.907	
Recurrent	70.7	75.1	63.8	75.2	65.8	53.7	62.2	64.5	0.814	0.093

Abbreviations: PF = physical functioning; SF = social functioning; RP = role – physical; RE = role – emotional; MH = mental health; VT = vitality; BP = bodily pain; GH = general health

Utility for conservative care

As mentioned previously, conservative care was modelled separately to the main analysis. The difference in utility between patients undergoing surgery and conservative care was used to calculate the difference in QALYs over time between these two treatments. The difference in utility between these two treatments was taken from Michaels and colleagues[170] (see Table 122), as this was the only paper found to report such data. Utility values are given at baseline, 1 month, 6 months, 12 months and 24 months post treatment; however by the 24 month follow-up, a large proportion of individuals had been lost to follow-up, and an unexpected large jump in utility is reported. This data was included in the base case analysis, and sensitivity analyses investigated the impact of omitting this 24 month data and extrapolating from the 12 month follow-up. The 1 month data was not included, as the GDG did not consider data collected within 3 months post treatment to be reliable, and because short term follow-up utility data was not included for the other treatment modalities. The difference in utility was adjusted for the difference at baseline, and changes in utility over time (for example between baseline and 6 months) were assumed to be gradual and linear. For the probabilistic analysis the difference between utility following conservative care and surgery was modelled using a Normal distribution to allow positive and negative differences.

L.2.3.4 Resource use and costs

Costs were associated with the following health states: initial treatment episode, physical symptoms with recurrent VVs (1), second treatment episode and physical symptoms with recurrent VVs (2). The cost of the initial and second treatment episodes included the cost of a main treatment, as well as top-up treatment where applicable. The costs borne in the recurrent VVs states when no interventional treatment was being delivered were due to the on-going costs of conservative care given to people in those states.

Cost of interventional treatments

NHS reference costs do not distinguish between the different varicose vein treatments, but rather an overall cost is given for primary unilateral varicose veins procedures (differs whether the procedure is conducted as a day case, outpatient procedure etc.). Consequently NHS references costs could not be used to capture the different costs of the treatments.

A review of existing economic literature was conducted in order to identify the costs of the various treatments. Five UK studies[30,106,143,170,257] were identified (See Table 125).

Table 125: UK relevant cost estimates from existing economic literature

Study	Surgery	Endothermal	FS	CC	Costing technique
Bountouroglou 2006[30]	£1,120.64	NA	£672.97	NA	Costs collected alongside RCT
Gohel 2010[106]	£980	EVLA £1,524 RFA £776	£202	£0	Based on NHS reference costs, adapted with additional information from manufacturers and list prices.
Lattimer 2012[143]	NA	£724.72 (£676.74 - £773.85)[1]	£126.39 (NR)[1]	NA	Costs collected alongside RCT
Michaels 2006[170] and Ratcliffe 2006[223]	£642.66 (236.39)[2]	NA	NA	£267.52 (350.91)[2,3]	Costs collected alongside RCT
Subramonia 2010[257]	£559.13	£1,275.90	NA	NA	Costs collected alongside RCT

All costs are mean initial treatment costs unless specified. Abbreviations: FS = foam sclerotherapy; CC = conservative care

[1] *Median (interquartile range)*

[2] *Mean costs from group 3; severe varicose veins randomised to surgery or conservative care (SD).*

[3] *Total undiscounted cost to NHS over 24 month period*

It is clear from Table 125 that cost estimates obtained from the literature varied considerably, and as such the GDG did not think these costs to be a reliable representation of UK practice. GDG members attempted to gather cost information from their trusts, but there was inconsistency in how these estimates were derived, so the GDG decided to construct cost estimates using a bottom up approach.

Resource use was therefore based on GDG estimates. Where possible, unit costs for these resources were collected from nationally available lists such as the NHS reference costs, or the PSSRU. However, it was not always possible to find such costs, and in such cases unit costs were based on GDG estimates. The cost estimates for the model are presented in the subsequent sections. The estimates were intended to capture the differences between the costs, and therefore some aspects (for example the cost of the initial appointments), have been omitted, as these are assumed not to differ greatly between treatments. The cost of compression following treatment was limited to bandages (applied immediately) and one pair of stockings, in line with the recommendation that prolonged compression should not routinely be provided.

The majority of the unit costs provided below do not have an associated measure of uncertainty and were therefore not modelled probabilistically. Probabilistic modelling was possible where unit costs were taken from the NHS reference costs; a gamma distribution was fitted by manually adjusting the standard error of the mean until the interquartile range of the distribution best matched that reported for the unit cost. A gamma distribution was chosen so that the distribution was constrained at zero (to avoid negative costs) and reflect the positive skew normally seen in cost data. Total costs were subject to extensive deterministic sensitivity analyses.

Surgery

The breakdown of costs for surgery is provided in Table 126.

The GDG noted that greater perioperative care would be needed with surgery than with the other treatments, thus a perioperative care estimate was included. No reliable figure was available to reliably cost a few extra hours spent on a ward, thus the Band 5 time which would be spent looking after a surgery patient was used as a proxy to capture the difference in perioperative care between different treatments.

Table 126: Costs - Surgery

Components	Unit cost	Hours/units Required	Point estimate	Distribution	Source
Pre-op assessment (Band 5)	£82.00	0.25 hours	£20.50	NA	PSSRU[62]
Band 5	£82.00	1 hours	£82.00	NA	PSSRU[62]
Band 5 (anaesthetic assistant)	£82.00	1 hours	£82.00	NA	PSSRU[62]
Healthcare Assistant Band 3	£20.00	1 hours	£20.00	NA	PSSRU[62]
Consultant: surgical	£136.00	1 hours	£136.00	NA	PSSRU[62]
Consultant anaesthetist	£136.00	1 hours	£136.00	NA	PSSRU[62]
Disposables[a]	£250.00	1	£250.00	NA	GDG estimate
Duplex	£52.84	1	£52.84	Gamma	NHS reference costs[77]
Stockings	£5.99[3]	1	£5.99	NA	Cost of TED stockings: NHS supply chain catalogue[187]
Perioperative care					
Band 5[b]	£82.00	1.5 hours	£123.00	NA	PSSRU[62]
Total			**£908.33**		

[a] *Includes gowns, surgical instruments, drapes, bandages and other disposable items*

[b]*Based on 90mins pre-op where patient is looked after by ¼ nurse, 30 minutes post-op where patient is looked after by 1 nurse, additional 150mins post op ¼ nurse time*

Endothermal techniques

The majority of the cost components for the two types of endothermal treatment (RFA & EVLA) were considered to be the same as each other, with the only differences being the cost of the generators, catheters and the controlled laser area required for EVLA. The cost of the catheter and generator vary, as commercial companies have individual contracts with different trusts. The costs in Table 127 have been provided by commercial companies; due to the business sensitive nature of this information individual company names have been removed.

Table 127: Catheter costs for EVLA and RFA

Procedure	Company	Generator cost	Catheter cost
EVLA	Company A	Provided on long term loan free of charge (List price is £15,000 - £22,000 but very rarely bought)	£180 - £245
	Company B	Provided on long term loan free of charge (List price is £12,500 but very rarely bought)	£200
RFA	Company C	Provided on long term loan free of charge	£300
	Company D	Provided on long term loan free of charge (List price is £10,000 but very rarely bought)	£250 - £300

As indicated in Table 127, in the vast majority of cases the generator is loaned free of charge, usually on the condition that the hospital carries out a certain amount of procedures per year. The cost of the generator was therefore not considered in the analysis. The costs of the catheters were approximated based on various estimates provided by commercial companies. Deterministic sensitivity analyses will investigate the impact of changes in cost of catheters.

The GDG decided not to explicitly include the cost of the controlled laser area needed for EVLA in the analysis, as the room would be used for a variety of laser procedures, and the cost per treatment would be highly dependent on the number of procedures undertaken.

In practice, the two endothermal treatments (EVLA and RFA) compete directly with each other, and this guideline assumes they have equal clinical effectiveness. The implication of this is that, in this analysis, whichever of these two treatments is the cheapest will be cost-effective. However, due to uncertainty around the costs, specifically that the RFA catheter is more expensive, but the EVLA requires a laser controlled area, it is not straight forward to identify which of these treatments is cheaper. For the purpose of this analysis it was assumed that once the cost of the laser controlled area had been accounted for, the costs of the two treatments would be similar. The cost of endothermal treatment used in the model was therefore £623.76. The breakdown of the costs is provided in Table 128.

Table 128: Costs – Endothermal treatment

Components	Unit cost	Hours/units Required	Point estimate	Distribution	Source
RFA catheter	£300	1	£300	NA	Table 127
EVLA catheter	£200	1	£200	NA	Table 127
Disposables[a]	£86.00	1	£86.00	NA	GDG estimate
Normal Saline £8.50 box of 20	£0.43	1	£0.43	NA	GDG estimate
Band 5	£82.00	0.75 hours	£61.50	NA	PSSRU[62]
Healthcare Assistant Band 3	£20.00	0.75 hours	£15.00	NA	PSSRU[62]
Consultant	£136.00	0.75 hours	£102.00	NA	PSSRU[62]
Duplex	£52.84	1	£52.84	Gamma	NHS reference costs[77]
Stockings	£5.99	1	£5.99	NA	NHS supply chain catalogue[187]
RFA Total			**£623.76**		
EVLA Total			**£523.76 + laser controlled area**		

(a) includes gowns, procedure pack, surgical instruments, drapes, bandages, syringes and other disposable items

Foam sclerotherapy

The breakdown of costs for Sclerotherapy is provided in Table 129.

Table 129: Costs - Sclerotherapy

Components	Unit cost	Hours/units Required	Point estimate	Distribution	Source
Consultant time	£136.00	0.75 hours	£102.00	NA	PSSRU[62]
Clinical nurse specialist time	£91.00	0.75 hours	£68.25	NA	PSSRU[62]

Components	Unit cost	Hours/units Required	Point estimate	Distribution	Source
Disposables[a]	£50.00	1	£50.00	NA	GDG estimate
Stockings (class II)	£42.30	1	£42.30	NA	NHS drug tariff[186]
Duplex	£52.84	1	£52.84	Gamma	NHS reference costs[77]
Total			**£315.39**		

(a) Includes gown, needles, bandages, syringes and other disposable items

Conservative care

The breakdown of costs for conservative care is provided in Table 130.

Based on clinical opinion, it was assumed that half of the patients who receive conservative care return to their GP in the first year for further advice and reassurance. After the first year, the annual costs were based on the assumption that the patient visits the practice nurse for a few routine appointments over the course of the year, for advice and to be re-measured for stockings. We acknowledge that in practice some of this measuring may be done by a pharmacist.

Table 130: Costs – Conservative care

Components	Unit cost	Hours/units required	Point estimate	Source
First year costs				
GP visits	£30.00	0.5	£15.00	PSSRU[62]
Annual costs				
Practice nurse time	£43.00	1.5 hours	£64.50	PSSRU[62]
Stockings (class II)	£42.30	4[a]	£169.20	NHS drug tariff[186]
First year total			**£248.70**	
Annual total			**£233.70**	

(a) based on an estimated lifespan of three months per stocking

Additional costs of retreatment

There are likely to be additional costs associated with re-treatment, over and above the cost of the second treatment itself. The additional costs associated with a second treatment episode were based on clinical opinion, and are provided in Table 131.

Table 131: Additional costs for retreatment

Components	Unit cost	Hours/units required	Point estimate	Distribution	Source
GP visit	£30.00	2.5	£75.00	NA	PSSRU[62]
OP 1st attendance vascular surgery	£165.49	1	£165.49	Gamma	NHS reference costs[77]
OP 2+ attendance vascular surgery	£123.28	1	£123.28	Gamma	NHS reference costs[77]
Duplex scan	£52.84	1	£52.84	Gamma	NHS reference costs[77]
Total			**£416.61**		

Note the resource components here have been replicated from the aforementioned on-going HTA project[239]

L.2.4 Sensitivity analyses

The sensitivity analyses described in Table 132 were undertaken to explore the effect of different parameter inputs and assumptions on the results of the model. The results of all sensitivity analyses are presented in section L.3.1.

Table 132: Alternative values and descriptions for deterministic sensitivity analyses

Analysis	Parameter	Description of sensitivity analysis	Values	Comment
SA1	Baseline recurrence rate	Some members of the GDG felt that the baseline recurrence rate following surgery, to which the relative effects from the NMA were applied, was too high. The baseline rate was calculated from clinical recurrence reported in randomised trials, and could be higher than those observed in UK practice for several reasons. Sensitivity analyses employ different baseline rates of recurrence	0.00384	Recurrence rate from Shadid2012[244] (lowest recurrence rate from included trials)
			0.01548	Recurrence rate from Carradice2011[48] (highest recurrence rate from included trials)
SA2	Endothermal treatment without concurrent phlebectomy	The need for top up treatment and cost of procedure is likely to be different if concurrent phlebectomy is not carried out. This sensitivity analysis evaluates the cost effectiveness of endothermal treatment without phlebectomies compared to the other treatments	10% require top up treatment Cost of procedure: £272.27 + catheter	The need for top up treatment will be higher, and the cost of procedure will be slightly lower; clinical evidence does not distinguish between endothermal with/without phlebectomy thus probability of clinical recurrence remains unchanged
SA3	Utility for conservative care	The data used for utility of conservative care includes a sharp increase in utility at 2 years. This increase is dramatic and unexpected, thus in this SA we omit the two year data	1 year adjusted difference between utility of conservative care and surgery: -0.1	The adjusted value reported at one year is extrapolated over the 5 year time horizon
SA4	GSV + SSV	Treating an additional truncal vein will extend procedure time and have an impact on total procedure cost	S: £1,119.12 F: £329.84 E: £691.27	Cost increase compared to base case due to an extra 15 minutes treatment time
SA5	Time horizon	The time horizon is shortened to avoid extrapolation past the maximum follow-up time found in the data	3 years	3 years is the longest follow-up of the trials included in the NMA
SA6	Costs	Various SAs to investigate how robust the model is to the costs of treatment, around which there is great uncertainty	Relative costs manipulated and costs for conservative care reduced	The GDG had no strong indication of what plausible ranges for treatment costs were; therefore threshold analyses conducted within an arbitrary but wide interval
SA6b	Cost of catheters for	These SAs investigate how robust the model is to	EVLA catheters:	Maximum and minimum values (as at

Analysis	Parameter	Description of sensitivity analysis	Values	Comment
	endothermal treatment	the costs of the endothermal catheters, around which there is great variability	£180-£245 RFA catheters: £250-£300	October 2012) provided by commercial companies
SA7	Top-up treatment rates	These SAs explore the impact of the GDG estimate of the proportion of patients who will need top up treatment	S: 0-5% F: 10-100% E: 0-5%	Threshold sensitivity analyses within plausible range suggested by GDG members
SA8	Proportions receiving conservative care following clinical recurrence (instead of re-treatment)	The proportion receiving a conservative care following clinical recurrence is varied (the remainder receive a second treatment episode)	75% 50%	Arbitrary, wide ranging values.
SA9	Proportions receiving each type of treatment during the second treatment episode	The type of retreatment a patient would receive would be highly dependent on the nature of the recurrence and further patient characteristics. This SA investigates the impact of the assumptions around the proportions of patients receiving each type of retreatment	S:20%; F:10%, E:70% S:5%; F:5%, E:90% S:10%; F:45%, E:45% S:15%; F:80%, E:5% S:10%; F:60%, E:30% S:10%; F:50%, E:40%	Sensitivity analyses use alternative proportions suggested by individual GDG members.

Abbreviations: F = Foam; S= Surgery; E= endothermal

L.2.5 Bilateral treatment

The model base case only considered unilateral patients, yet consideration should also be given to treatment of bilateral patients. The model does not lend itself to bilateral analysis, as significant assumptions would have to be made around whether top-up treatment was complete in one or two legs, whether clinical recurrence was experienced in one or two legs, and whether both legs were retreated. Furthermore, utility increases and decrements as used in the unilateral model would no longer be applicable. The GDG therefore decided that a cost-comparison was the preferred method to analyse the treatment of bilateral patients.

In order to calculate costs of bilateral surgery and endothermal treatment, a proportional increase was applied to the unilateral costs documented in Table 126 and Table 128. A variety of scenarios were presented in which this proportional increase was varied, in order to capture uncertainty. The maximum that bilateral treatment could be expected to cost would be 200% of the cost of unilateral treatment, as would be the case if both legs were to be treated completely separately. Therefore the maximum cost of bilateral treatment was assumed to be 200% of the costs specified in Table 126 Table 128. The NHS reference costs[77] indicate that for day case procedures, bilateral treatment costs 112% of the cost of unilateral treatment; this was taken as the minimum proportional increase in costs.

The bilateral cost of foam sclerotherapy was assumed to be twice the cost of unilateral treatment. This is because there are consensus recommendations on the maximum amount of sclerosant foam which should be given per session.[36] The recommended maximum volume per session is 10ml, and the recommended average is lower, between 2 and 8ml of sclerosant foam. In many cases this would prevent treatment of both legs in one sitting; indeed the recommendations add that it is advisable to limit the amount of sclerosant foam given per session, even if this means the patient requires more than one treatment. As the costs of initial appointment have been omitted, treating the legs separately can be considered equivalent to two unilateral cases from a costing point of view.

The cost of conservative care for bilateral treatment was calculated by doubling the number of stockings required. The number of GP appointments and practice nurse time was assumed to stay the same as with unilateral treatment.

The results of the cost comparison are documented in section L.3.2.

L.2.6 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation.

L.2.6.1 Calculating cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not applicable.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs/QALYs(X) = total costs/QALYs for option X

- Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs for the remaining options.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: Costs/QALYs(X) = total costs/QALYs for option X; λ = threshold

- Cost-effective if: highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB was used to identify the optimal strategy in the probabilistic analysis simulations.

The probabilistic analysis was run for 10,000 simulations. Each simulation, total costs and total QALYs were calculated for each strategy. Net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 per QALY gained. The results of the probabilistic analysis were summarised in terms of mean costs, mean QALYs and mean net benefit for each treatment option, where each was the average of the simulated estimates. The option with the highest mean net benefit (averaged across the simulations) was the most cost-effective at the specified threshold. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Results are also presented graphically where mean total costs and mean total QALYs for each treatment option is plotted. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio, the magnitude of which is labelled.

L.2.7 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by an experienced health economist who had not been involved in the guideline; this included systematic checking of the model calculations.

L.2.8 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

L.3 Results

Detailed results are presented over the next few pages for the base case and various sensitivity analyses. As the results of the deterministic and probabilistic analysis were comparable, all results reported below are means from the probabilistic analysis unless otherwise specified.

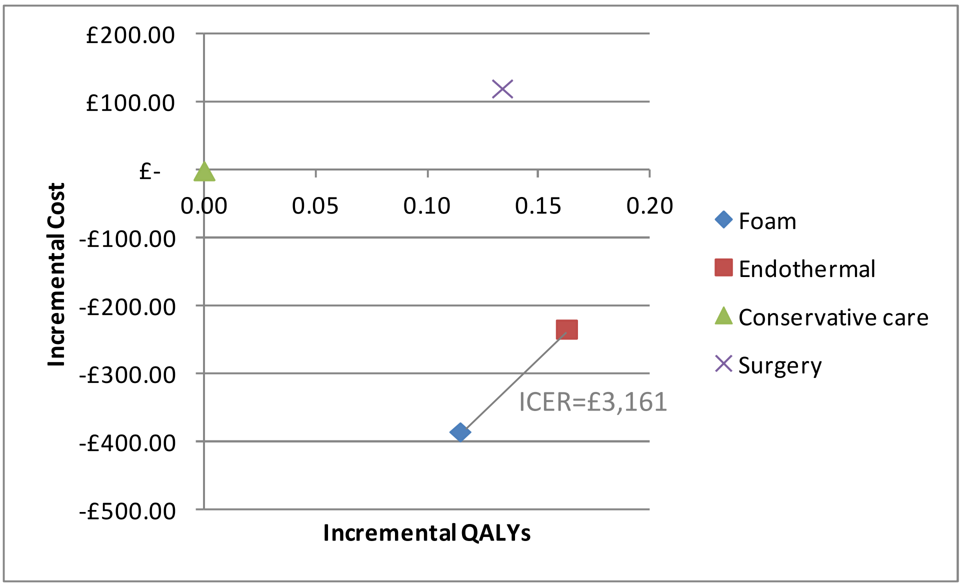
Table 133 and Figure 161 show the base case results. Both conservative care and surgery were dominated, as they provided less QALYs at increased cost when compared to endothermal treatment. As these strategies are dominated, they are not further considered in the incremental analysis and the ICER is not calculated.

Table 133: Mean base case results (probabilistic)

Treatment	Mean per patient		NMB at threshold of £20,000	Rank at threshold of £20,000	Probability of being CE[a]
	QALYs	Cost			
Conservative care	3.55	£1,102	£69,965	4	4%
Surgery	3.69	£1,222	£72,554	3	3%
Foam sclerotherapy	3.67	£718	£72,681	2	23%
Endothermal	3.72	£869	£73,484	1	71%

(a) For interpretation of the probability of being cost-effective see section L.2.6.1.

Figure 161: Cost effectiveness plane showing incremental cost and QALYs per patient expected with each strategy (Base case, probabilistic analysis)



In the base case analysis, the strategy which provided the most QALYs was endothermal treatment. However, this came at an additional cost compared to foam sclerotherapy. Using the mean costs and QALYs generated over the probabilistic sensitivity analysis, the ICER of endothermal treatment compared to foam was £3,161 which is below the NICE threshold of £20,000 per QALY gained. Endothermal treatment had a probability of being cost-effective of 71%, followed by foam which had a lower chance of being the most cost-effective option of 23%.

Disaggregating the results of the analysis by cost and QALYs allows us to examine the impact of key components of the model on the overall results. The QALYs associated with the initial treatment episode are the same for each treatment, therefore we know that that the difference in total QALYs is driven by the reduction in QoL associated with recurrence. Endothermal treatment has the lowest probability of recurrence per cycle, thus the results of the model align with our expectation that this treatment would lead to the highest total QALYs.

Table 134 provides the breakdown of total cost (the probabilistic costs of the initial treatment episode are comparable to the deterministic estimates in Table 126 –Table 130). It shows that whilst the costs due to recurrent treatment do differ (Note – this is the cost of retreatment averaged across all patients), the difference in total costs between treatment methods is mainly due to the initial treatment costs. Sensitivity analyses explored the impact of changes in the treatment costs – see below.

Table 134: Breakdown of total costs (probabilistic base case)

Treatment	Cost of initial treatment episode	Cost of recurrent treatment[a]	Total cost
Conservative care[b]	N/A	N/A	£1,102
Surgery	£924	£299	£1,222
Foam sclerotherapy	£378	£340	£718
Endothermal	£639	£230	£869

(a) This is the average cost of treatment and management of recurrent varicose veins weighted by the proportion of individuals who will require this, therefore this represents the expected per person cost of recurrence.

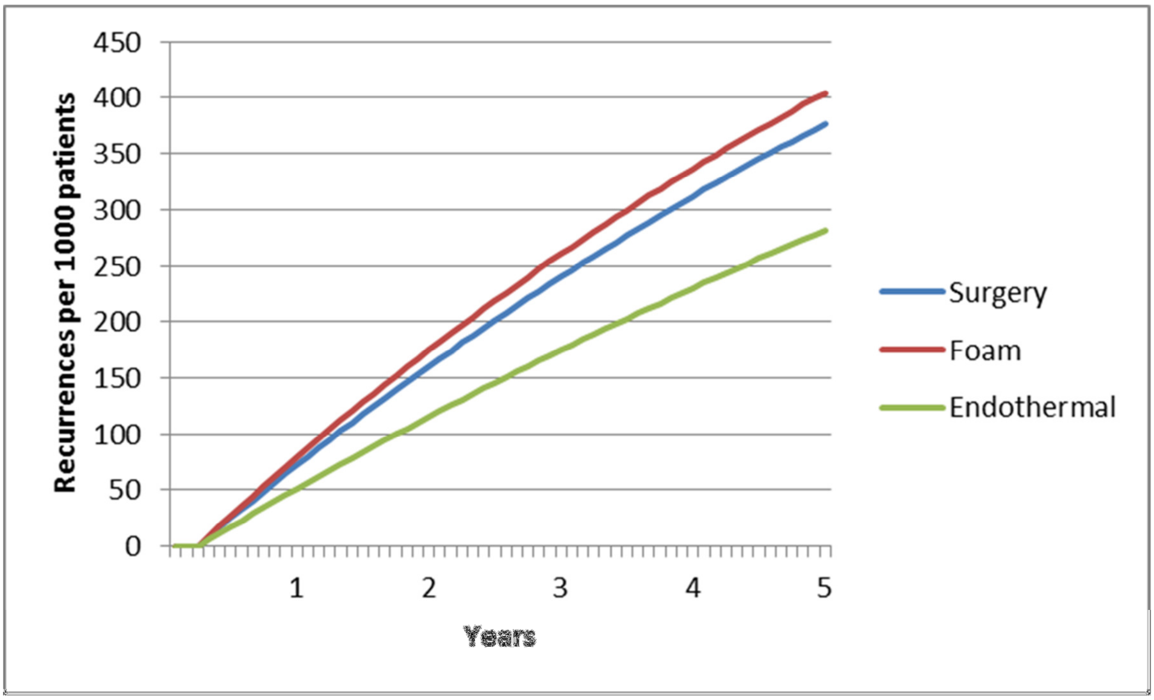
(b) Initial and recurrent treatment costs are not applicable for conservative care as this was modelled separately as an on-going management technique

The number of clinical recurrences over time is shown in Figure 162 for each treatment. The GDG felt these values were acceptable, but noted that it was difficult to judge face validity of these results, as the majority of the GDG members do not see all clinical recurrence cases, only those patients who are to be retreated. Sensitivity analyses investigated the impact of changing the level of clinical recurrence.

L.3.1 Sensitivity analyses

Sensitivity analyses were run probabilistically unless otherwise stated. In all analyses endothermal treatment was recorded as the optimal strategy. Table 136 summarises the results of these analyses. Throughout all of the probabilistic sensitivity analyses, neither the probability of conservative care or surgery being the optimal strategy rose above 5%. Overall, the sensitivity analyses demonstrated that the results of this analysis were robust to changes in key assumptions, recurrence rates, and substantial changes in relative costs.

Figure 162: Clinical recurrence over time



L.3.2 Bilateral treatment

The results of the cost comparison are presented in Table 135. The GDG discussed the figures in this table alongside the bilateral results, and concluded that endothermal treatment is likely to be the cost-effective treatment strategy for bilateral treatment.

Table 135: Bilateral treatment cost comparison (deterministic)

Cost of unilateral treatment	Multiplier	Cost of bilateral treatment
Conservative care		
£234[a]	NA	£403[a]
Surgery		
£924	112%	£1,035
	120%	£1,109
	140%	£1,294
	160%	£1,479
	180%	£1,663
	200%	£1,848
Endothermal		
£640	112%	£716
	120%	£767
	140%	£895
	160%	£1,023
	180%	£1,151
	200%	£1,279
Foam sclerotherapy		
£378	200%	£757

(a) represents annual cost

Table 136: Results of sensitivity analysis

	Mean QALYs per patient				Mean costs per patient					
Sensitivity analysis	**CC**	**S**	**FS**	**E**	**CC**	**S**	**FS**	**E**	**Optimal strategy**	**Probability CE at £20,000 threshold**
SA1 : Baseline recurrence rate										
SA1a: Lowest baseline recurrence	3.62	3.75	3.74	3.77	£1,102	£1,067	£548	£746	Endothermal	74%
SA1b: Highest baseline recurrence:	3.48	3.61	3.59	3.66	£1,102	£1,402	£901	£1,015	Endothermal	74%
SA2 – SA5: Assumptions										
SA2: Endothermal treatment does not include phlebectomy	3.55	3.69	3.67	3.72	£1,102	£1218	£713	£822	Endothermal	73%
SA3: Utility for conservative care extrapolated from 1 year value	3.25	3.69	3.67	3.72	£1,102	£1224	£722	£871	Endothermal	75%
SA4: GSV + SSV	3.55	3.69	3.67	3.72	£1,102	£1355	£805	£943	Endothermal	72%
SA5: 3 year time horizon	2.19	2.32	2.31	2.33	£699	£1085	£569	£761	Endothermal	62%
SA6: Costs (deterministic)										
SA6i: Surgery, sclerotherapy, conservative care costs reduced by 50%, cost of endothermal remains as base case	3.56	3.69	3.68	3.73	£558	£687	£432	£789	Endothermal	N/A
SA6ii: Below knee standard stockings for conservative care (£11 instead of £42 per pair)	3.56	3.69	3.68	3.73	£511	£1,179	£653	£828	Endothermal	N/A
SA6iii: Below knee standard stockings and no practice nurse time for conservative care	3.56	3.69	3.68	3.73	£211	£1,162	£635	£816	Endothermal	N/A
SA6iv: Threshold cost analysis of increase in cost of	The cost of endothermal treatment would have to increase by £681, and the cost of all other treatments remain the same in order to no longer be considered cost-effective. In this instance, foam would be the optimal strategy.									

Sensitivity analysis	**Mean QALYs per patient**				**Mean costs per patient**				**Optimal strategy**	**Probability CE at £20,000 threshold**
	CC	**S**	**FS**	**E**	**CC**	**S**	**FS**	**E**		
endothermal treatment										
SA6b: Cost of catheters for endothermal treatment										
£180	3.55	3.69	3.67	3.72	£1,102	£1,209	£703	£738	Endothermal	74%
£395	3.55	3.69	3.67	3.72	£1,102	£1,233	£730	£970	Endothermal	67%
SA7: Top-up treatment rate - threshold analyses (deterministic)										
Surgery 0-10%	N/A								Endothermal	N/A
Foam sclerotherapy 10-100%	N/A								Endothermal	N/A
Endothermal 0-10%	N/A								Endothermal	N/A
SA8: Proportions receiving conservative care following first recurrence instead of retreatment										
SA8a: 75%	3.53	3.66	3.64	3.70	£1,102	£1,159	£648	£820	Endothermal	72%
SA8b: 50%	3.54	3.68	3.66	3.71	£1,102	£1,191	£682	£844	Endothermal	72%
SA9: Proportions receiving each type of treatment during the second treatment episode (deterministic)										
S:20%; F:10%; E:70%	3.56	3.69	3.68	3.73	£1,102	£1,235	£714	£869	Endothermal	N/A
S:5%; F:5%; E:90%	3.56	3.69	3.68	3.73	£1,102	£1,227	£706	£863	Endothermal	N/A
S:10%; F:45%;E:45%	3.56	3.69	3.68	3.73	£1,102	£1,208	£685	£849	Endothermal	N/A
S:15%; F:80%; E:5%	3.56	3.69	3.68	3.72	£1,102	£1,192	£668	£837	Endothermal	N/A
S:10%; F:60%; E:30%	3.56	3.69	3.68	3.72	£1,102	£1,200	£676	£843	Endothermal	N/A
S:10%; F:50%; E:40%	3.56	3.69	3.68	3.73	£1,102	£1,206	£682	£847	Endothermal	N/A

L.4 Discussion

L.4.1 Summary of results

This analysis found that endothermal treatment is the most clinically and cost effective treatment strategy for people with varicose veins (note - EVLA and RFA were considered together in the model, and the results do not distinguish between these two endothermal techniques). This conclusion was robust to a wide range of sensitivity analyses, demonstrating that although uncertainty surrounds model inputs, variation within reasonable ranges does not change the results.

An area of particular uncertainty was the costs, yet sensitivity analyses revealed that the model is robust to changes in relative costs. For example, even if the differences in costs have been underestimated, endothermal treatment would remain the optimal strategy even if the costs of all the other treatments are half of what we estimated in the base case. If the costs of surgery, sclerotherapy and conservative care remain as specified in the base case, endothermal treatment remains cost effective even with increases in cost of up to £681.

L.4.2 Limitations and interpretation

The clinical review was not designed to distinguish between different types of endothermal treatment and as such the results presented here do not make any distinction between RFA and EVLA, or any further variation within these treatment modalities. Whilst the decision to treat the various endothermal treatments as one combined treatment was based on GDG consensus, this could be considered a limitation of the analysis.

A further limitation of the model is the specific population to which it applies. The interventions considered are only true comparators when considering patients for whom all four treatments are a possibility, and in practice this may only be a small proportion of the varicose veins population. If endothermal treatment is not suitable for a patient then foam sclerotherapy is the cost-effective option, and if foam is not suitable either, surgery is the optimal strategy. Further issues of generalizability are discussed in section L.4.3.

An additional drawback of this analysis is that the estimates of rates of top-up treatment were based on GDG estimates, but the clinical recurrence data was based on trial outcomes. Depending on how clinical recurrence was reported, it is likely that in some instances the trials recorded what would be deemed here as a need for top-up treatment as clinical recurrence. The implication of this is that some recurrences may have been double counted. This said, sensitivity analyses revealed that the model was robust to changes in top-up rates and in clinical recurrence rates, therefore this drawback represents only a minor limitation.

Assumptions were made around top-up treatments, as well as modality of retreatment, which could potentially be considered as limitations to the model. However sensitivity analyses revealed that reasonable changes in these assumptions did not impact the results.

The assumptions of the network meta-analysis model necessitated a constant hazard of clinical recurrence over time. This represents a restriction of the analysis, yet this assumption was deemed reasonable over the relatively short time horizon of the model. Ideally, utility data would have been included which reflected treatment specific improvements in quality of life, however as discussed earlier, reliable data to reflect this could not be found. Use of the PROMs data brings its own limitations, such as the potential for sampling bias.

Finally, this analysis does not attempt to answer the questions of the optimal timing of intervention, or the optimal choice of treatment at each stage of the disease. We initially hoped to address these questions, but reliable data were not available. Consequently, conclusions are applicable to the general varicose veins population, with no separate consideration of subgroups. Input data were collected from individuals at various stages of varicose veins severity, and we cannot be certain that interventional treatment is cost-effective in each subgroup.

L.4.3 Generalisability to other populations / settings

The conclusions of this analysis are expected to apply to the UK adult varicose veins population. Whilst varicose veins are only rarely seen in children, the results of this analysis are unlikely to be generalisable to this population.

Endothermal treatment and foam sclerotherapy were assumed to take place in an outpatient setting and surgery as a day case procedure. The analysis has not considered different settings of treatment, for example endothermal treatment as a day case procedure or surgery as an inpatient procedure. Nevertheless, sensitivity analysis did show that the optimal strategy was fairly robust to increases in the cost of endothermal treatment and so if outpatient endothermal treatment was not considered suitable for a patient, day case endothermal treatment may represent a cost-effective alternative.

L.4.4 Comparisons with published studies

Gohel and colleagues (2010)[106] present the only analysis published at present which compares all the treatments included in this analysis in a UK setting. Whilst day case surgery offers the highest net benefit, the authors conclude that RFA or EVLA performed as an outpatient procedure, or surgery performed as a day case procedure, are likely to be cost-effective treatments, as differences in costs and QALYs are small. The suggestion that RFA and EVLA are cost-effective aligns with our findings that endothermal treatment is the optimal treatment strategy.

L.4.5 Conclusion = evidence statement

According to the results of this original economic model based on the current clinical evidence review and GDG input, it is likely that endothermal treatment is the cost effective strategy for people in whom all treatments are suitable. When endothermal treatment is not deemed suitable for a patient, foam sclerotherapy is likely to be the optimal strategy. Surgery represents the optimal choice if neither endothermal treatment nor foam sclerotherapy are thought suitable. This evidence is directly applicable, with minor limitations.

L.4.6 Implications for future research

A major issue which remains to be addressed is the question of which patients should be treated, which is closely related to the question of the optimal timing of intervention. To answer such a question would require data on the natural progression of varicose veins, i.e. what happens to patients who are not treated. Such data is unlikely to emerge from future research due to ethical considerations.

Future research into the effectiveness of each intervention at each stage of the disease would be a step towards solving this issue. If this data was available, future analyses could investigate whether different treatment strategies are optimal at different stages of the disease, and potential efficiencies could be realised.

Appendix M: Network meta-analysis

M.1 Network meta-analysis code

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                   # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {           # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
```

```
    }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { cloglog(T[k]) <- log(timeA) + A + d[k]  }
# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lhr[c,k] <- (d[k]-d[c])
log(hr[c,k]) <- lhr[c,k]
}
}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
}                    # *** PROGRAM ENDS
```

M.2 Baseline model code (meta-analysis of surgery trial arms)

```
# Random effects probability model
model{
for( i in 1 : 8) {
   r[i] ~ dbin(p[i],n[i])                    #Likelihood
   cloglog(p[i]) <- b[i] + log(time[i])                                 #cloglog of response
   b[i] ~ dnorm(d,prec)    #Random effects model
   rhat[i] <- p[i] * n[i] # expected value of the numerators
#Deviance contribution
  dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
      +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
 }
b.new~dnorm(d,prec)    #predictive dist. (log-odds)
resdev <- sum(dev[])
d ~ dnorm(0.0,1.0E-6)  #vague prior for mean effect

cloglog(T1) <- b.new +log(1)
cloglog(T12) <- b.new +log(12)
cloglog(T24) <- b.new +log(24)
cloglog(T36) <- b.new +log(36)

#logit(T.new) <- b.new
#sd <- 1/sqrt(prec)     # gamma prior for RE precision
#prec ~ dgamma(0.001,0.001)
sd ~ dunif(0,5)       # uniform prior for RE st dev
prec <- pow(sd,-2)
}
```

Appendix N: Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

N.1 Key future research recommendations (FRR)

N.1.1 Natural history of varicose veins

In people with varicose veins at CEAP (Clinical, etiological, anatomical and pathophysiological) stage C2 or C3, what are the factors that influence progression of the disease to CEAP stages C5 or C6?

Why this is important

The evidence review for the guideline showed a lack of high-quality evidence on the progression of varicose veins from CEAP stage C2 or C3 to more serious varicose veins disease. A large observational prospective cohort study, similar to the Framingham or BONN veins studies, should be undertaken. The study should recruit patients with C2 and C3 disease and follow the progress of their disease over a number of years. Consideration should be given to including a genetic component in the study because genetic factors have not been studied on a large scale. The results of such a study should help to more accurately identify which patients are at risk of developing more serious disease so that interventions can be offered at an early stage to those who will benefit most.

Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	If the research were to identify clear factors which were indicators for progression to more serious disease, those patients who are most at risk could be identified at an earlier stage and either monitored more closely or treated at an earlier stage. This would then potentially lead to more efficient use of resources.
Relevance to NICE guidance	This research is of medium relevance to the NICE guidelines. The research is relevant but is not key to future updates as a recommendation was able to be produced in its absence.
Relevance to the NHS	The research is relevant to the NHS, depending on the results it may allow the identification of people at risk, and hence may change the allocation of resources.
National priorities	This research is not relevant to a national priority area.
Current evidence base	The evidence found from the systematic reviews in the guideline were mainly case control and small cohort studies. These are not sufficient to identify all the risk factors. In addition, no large scale study has looked to determine if there is a genetic component involved in the progression of varicose veins.
Equality	The research would not discriminate against any group.
Feasibility	The proposed research is a long term project and does have a substantial cost associated

Criterion	Explanation
	with it. However, it was the opinion of the GDG that the potential benefits of the research would outweigh the costs. The issue of treatment needs to be considered. It would not be ethical to prevent patients from having treatment as their disease worsened. Treatment should be taken into account in the research design.
Other comments	None
Study design	Prospective cohort study

N.1.2 Interventional treatment for those with CEAP stage C6 disease (leg ulcers) and varicose veins

Does the early interventional treatment of superficial venous reflux together with compression therapy improve wound healing and result in greater cost effectiveness compared with compression therapy alone in patients with chronic venous ulceration?

Why this is important

Chronic venous leg ulcers are a common major cause of morbidity. Quality of life for patients with venous leg ulcers is substantially reduced by discomfort and social isolation resulting from odour and wound discharge. The social and personal impact of chronic venous leg ulceration is therefore considerable.

Only one study has been completed in which surgery and compression were compared with compression alone. This showed improvement in the rates of ulcer recurrence. It would now be suitable to consider endovenous interventional techniques which, being a minimally invasive procedure, are more acceptable to patients.

At present ulceration is often managed with compression, despite poor success rates. A high-quality large-scale randomised trial evaluating outcomes after early interventional treatment compared with compression therapy is needed.

Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	This study is important to those patients with CEAP stage C6 disease whose quality of life is substantially reduced by discomfort and social isolation resulting from odour and wound discharge. The social and personal impact of chronic venous leg ulceration is therefore considerable.
Relevance to NICE guidance	Results would influence recommendations regarding best management of severe venous dysfunction and with the ESCHAR study would influence the planning of venous services.
Relevance to the NHS	Leg ulceration due to superficial venous reflux is a major cause of morbidity and a huge drain on NHS resources. Improved management techniques may influence service delivery and ultimately strategic planning.
National priorities	None
Current evidence base	The RCT ESCHAR study compared surgery and compression with compression alone but it might now be suitable to consider endovenous interventional techniques which being a minimally invasive procedure is more acceptable to patients and may be delivered

Criterion	Explanation
	without delay.
Equality	None identified.
Feasibility	The proposed research could be carried out within a realistic timescale and at an acceptable cost. No ethical or technical issues?
Other comments	This study has recently been submitted in the form of The Early Venous Reflux Ablation (EVRA) ulcer trial to the National Institute for Health Research. In the ESCHAR study, no improvement in ulcer healing rates was seen, but operative intervention was delayed for a median time of 7 weeks. Recruitment period : 24 months. Study duration : 48 months.
Study design	Multi-centred randomised controlled trial.

N.1.3 Truncal treatment with or without concurrent tributary treatment

Research Question

What is the clinical and cost effectiveness of concurrent phlebectomies for varicose tributaries during truncal endothermal ablation for varicose veins compared with:

- truncal endothermal ablation without concurrent phlebectomies
- truncal endothermal ablation with subsequent phlebectomies, if needed, 6–12 weeks later.

Why this is important

Conventional truncal stripping under general anaesthetic involves synchronous phlebectomies of varicose tributaries, and in ultrasound-guided foam sclerotherapy truncal and tributary veins are treated concurrently. In contrast, endothermal ablation may be performed alone to obliterate truncal incompetence, or synchronously with phlebectomies, and current practice varies.

Synchronous tributary treatment ensures a single treatment episode, and the removal of all symptomatic varicosities leads to a better immediate quality of life, but this takes longer and thus may be associated with increased morbidity. Deferred tributary treatment may reduce morbidity, and also mean that some patients do not need tributary treatment (or need fewer tributary treatments on smaller veins). However, it involves two interventions for patients who need tributary treatment. Omitting tributary treatments entirely ensures a single treatment episode, but it is unclear whether remaining varicosities will persist and impair quality of life.

At present there is limited evidence from one small-scale (n=50) study on the use and timing of tributary treatments after truncal endothermal ablation treatment. There is a need for practice to be based on empirical evidence from a large and sufficiently powered RCT comparing all three main intervention options (no tributary treatment, concurrent tributary treatment and delayed tributary treatment).

Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	If the trial showed a benefit of tributary treatment during or after treatment this would lead to altered guidance recommending tributary treatment during or after interventional treatment. This would improve patients' quality of life.
Relevance to NICE guidance	This research is of medium importance to the NICE guideline, as the research is relevant to the recommendations in the guideline but the research recommendations are not key to future updates.

Criterion	Explanation
Relevance to the NHS	The impact of this research on the NHS is minimal. If the research identified a benefit with tributary treatment during or after treatment a change in recommendation would be required which would lead to a change in practice in the NHS and could reduce costs.
National priorities	This research is not relevant to any known national priority areas.
Current evidence base	The evidence for this section was reviewed in chapter 9e. Only 1 randomised controlled trial was identified in this area. This was not prone to serious bias (unblinded, but clear allocation concealment and no attrition bias) but was possibly underpowered with high levels of imprecision for some outcomes, leading to these outcomes being graded as very low. In addition, this RCT had a short follow-up of only 6 weeks for concurrent tributary treatments vs. no tributary treatment.
Equality	The research does not address equality issues as all people will be able to access the intervention.
Feasibility	The research is expected to be able to be carried out within a realistic timescale and acceptable cost. It is not expected that there would be any ethical or technical issues.
Other comments	None
Study design	Randomised controlled trial

N.1.4 Compression as a management option

What is the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins?

Why this is important

Compression hosiery is widely used as first-line treatment for symptomatic varicose veins. In some areas of the UK a period of hosiery use is a precursor to referral to secondary care.

Discomfort and difficulty in application may cause people to stop wearing compression hosiery or wear it only occasionally. The current evidence for the benefit of compression hosiery is weak. There is little evidence of an impact on symptom relief or an improvement in quality of life. It is therefore not possible to calculate the cost effectiveness of compression hosiery.

A multicentre trial randomising compression hosiery versus no compression in patients with symptomatic varicose veins is needed. The trial should evaluate quality of life, including symptom reduction, and measure adherence with compression hosiery. In addition the trial should investigate the impact of compression on disease progression and the need for subsequent intervention.

Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	The research is important to patients and, if results showed a benefit for compression, clinicians would be confident they were being offered a clinically proven treatment option.
Relevance to NICE guidance	This research is highly relevant to NICE guidance. The answer to this question may change the guidance and the way that varicose veins are treated. The poor quality current evidence and relatively high costs mean that compression has not been

Criterion	Explanation
	recommended, but if the research were to identify that symptoms of varicose veins were substantially reduced the recommendation may change. Compression might then provide an effective non-interventional management strategy.
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)? The research could potentially reduce the variation in practice within the NHS. If the results showed that compression hosiery was effective for the management of varicose veins this would provide a non-interventional management strategy. Conversely, if the research was clear that compression stockings showed little benefit, the NHS could then stop prescribing an ineffective treatment benefit. In addition, if there was evidence concerning who benefited from compression hosiery, treatment could be better targeted.
`	This research is not likely to have an impact on national priorities.
Current evidence base	The systematic review of the evidence identified 3 low or very low quality RCTs, two of which were completed more than 15 years ago (see section 8.1). These investigated patient assessed symptoms and adverse events but did not look at patients' quality of life. In addition, 5 observational studies were identified which provided some further information. The GDG felt strongly that the nature of the evidence created much uncertainty about the results for all relevant outcomes.
Equality	Equality issues are not particularly relevant to this research question, although the ability to put on and take off compression hosiery and whether that had an impact in the adherence to the treatment strategy should be considered as part of the research
Feasibility	The proposed research is considered by the GDG to be feasible and able to be carried out within a realistic timescale and at an acceptable cost. There are no known ethical or technical issues.
Other comments	None
Study design	Randomised Controlled Trial

N.1.5 Compression after interventional treatment

What is the clinical and cost effectiveness of compression hosiery after interventional treatment for varicose veins compared with no compression hosiery? If there is benefit, how long should compression hosiery be worn for?

Why this is important

The benefit of compression after interventional treatment for varicose veins is unclear. A well conducted multicentre randomised controlled trial (RCT) of compression hosiery after each of the three main interventional treatments would help determine whether compression hosiery is beneficial, and if so, what type of compression is best and how long it should be worn for. There should be 6 RCT arms, one arm with compression and one arm without in each of three patient groups: patients who have had endothermal ablation, patients who have had ultrasound-guided foam sclerotherapy and patients who have had surgery. Each arm should have subgroups for compression type and duration. Adherence to treatment with compression hosiery and the effect of adherence on effectiveness should also be evaluated. A cost-effectiveness analysis should be performed. If compression hosiery is beneficial, such a trial should help improve quality of life for people with varicose veins and reduce the longer-term need for retreatment.

Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	If the trial showed a benefit of compression hosiery after treatment this would lead to altered guidance recommending compression after interventional treatment. This would improve patients' quality of life.
Relevance to NICE guidance	This research is of medium importance to the NICE guideline, as the research is relevant to the recommendations in the guideline but the research recommendations are not key to future updates.
Relevance to the NHS	The impact of this research on the NHS is minimal. If the research identified a benefit with compression after interventional treatment a change in recommendation would be required which would lead to a change in practice in the NHS.
National priorities	This research is not relevant to any known national priority areas.
Current evidence base	The evidence for this section was reviewed in chapter 10. Only 2 low / very low quality randomised controlled trials were identified in this area which were both prone to serious bias. In most cases the imprecision of the point estimate was too large to be able to confidently judge the magnitude/direction of the true population effect.
Equality	The research does not address equality issues as all people will be able to access the intervention. Patient compliance with compression should be assessed in the research to determine if there are any factors which meant that compression was not suitable for specific groups.
Feasibility	The research is expected to be able to be carried out within a realistic timescale and acceptable cost. It is not expected that there would be any ethical or technical issues.
Other comments	None

Criterion	Explanation
Study design	Randomised controlled trial

Appendix O: References

1 Endovascular radiofrequency ablation for varicose veins: An evidence-based analysis. Ontario Health Technology Assessment Series. 2011; 11(1):1-93

2 Abela R, Liamis A, Prionidis I, Mathai J, Gorton L, Browne T et al. Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard and invagination stripping: a prospective clinical series. European Journal of Vascular and Endovascular Surgery. 2008; 36(4):485-490

3 Abramowitz I. The treatment of varicose veins in pregnancy by empty vein compressive sclerotherapy. South African Medical Journal. 1973; 47(14):607-610

4 Alberta Heritage Foundation for Medical Research. Graduated compression stockings to prevent and treat venous insufficiency. Alberta, Canada. Alberta Heritage Foundation for Medical Research, 1997

5 Ali SM, Callam MJ. Results and significance of colour duplex assessment of the deep venous system in recurrent varicose veins. European Journal of Vascular and Endovascular Surgery. 2007; 34(1):97-101

6 Allegra C, Antignani PL, Carlizza A. Recurrent varicose veins following surgical treatment: our experience with five years follow-up. European Journal of Vascular and Endovascular Surgery. 2007; 33(6):751-756

7 Anderson JH, Geraghty JG, Wilson YT, Murray GD, McArdle CS, Anderson JR. Paroven and graduated compression hosiery for superficial venous insufficiency. Phlebology. 1990; 5(4):271-276

8 Antoch G, Pourhassan S, Hansen O, Stock W. Comparison of colour Doppler ultrasonography, ascending phlebography and clinical examination in the diagnosis of incompetent calf perforating veins. British Journal of Surgery. England 2002; 89(2):192-193

9 Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in Health. 2008; 11(7):1131-1143

10 Atkin GK, Round T, Vattipally VR, Das SK. Common peroneal nerve injury as a complication of short saphenous vein surgery. Phlebology. 2007; 22(1):3-7

11 Bachoo P. Interventions for uncomplicated varicose veins. Phlebology. 2009; 24(Suppl.1):3-12

12 Barrett JM, Allen B, Ockelford A, Goldman MP. Microfoam ultrasound-guided sclerotherapy treatment for varicose veins in a subgroup with diameters at the junction of 10 mm or greater compared with a subgroup of less than 10 mm. Dermatologic Surgery. 2004; 30(11):1386-1390

13 Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet. 2004; 363(9424):1854-1859

14 Basel H, Aydin C, Aya Y, Inan B, Ekim H, Goya C et al. Endovenous laser ablation (EVLA) versus high ligation and striping (HL/S): Two-years follow-up. Eastern Journal of Medicine. 2012; 17(2):83-87

15 Belcaro G, Cesarone M, Di Renzo A, Brandolini R, Coen L, Acerbi G et al. Treatments for varicose veins: Surgery, sclerotherapy, foam sclerotherapy and combined (surgery+sclerotherapy) options. A 10-year, prospective, randomised, controlled, follow-up study. The VEDICO* trial and EST (European Sclerotherapy Trial). Angeiologie. 2003; 55(1):29-36

16 Belcaro G, Cesarone MR, Di Renzo A, Brandolini R, Coen L, Acerbi G et al. Foam-sclerotherapy, surgery, sclerotherapy, and combined treatment for varicose veins: a 10-year, prospective, randomized, controlled, trial (VEDICO trial). Angiology. 2003; 54(3):307-315

17 Belcaro G, Dugall M, Vasdekis S, Christopoulos D, Laurora G, Nicolaides AN et al. Comparison between endovascular sclerotheraphy, surgery and surgery plus sclerotheraphy in the treatment of superficial vein insufficiency. A randomized study on 10 years follow-up. Angeiologie. 1998; 50(1):57-61

18 Belcaro G, Nicolaides AN, Ricci A, Dugall M, Errichi BM, Vasdekis S et al. Endovascular sclerotherapy, surgery, and surgery plus sclerotherapy in superficial venous incompetence: a randomized, 10-year follow-up trial--final results. Angiology. 2000; 51(7):529-534

19 Benigni JP, Sadoun S, Allaert FA, Vin F. Efficacy of Class 1 elastic compression stockings in the early stages of chronic venous disease. A comparative study. International Angiology. 2003; 22(4):383-392

20 Beresford SA, Chant AD, Jones HO, Piachaud D, Weddell JM. Varicose veins: a comparison of surgery and infection/compression sclerotherapy. Five-year follow-up. Lancet. 1978; 1(8070):921-924

21 Beresford T, Smith JJ, Brown L, Greenhalgh RM, Davies AH. A comparison of health-related quality of life of patients with primary and recurrent varicose veins. Phlebology. 2003; 18(1):35-37

22 Bernardini E, De Rango P, Piccioli R, Bisacci C, Pagliuca V, Genovese G et al. Development of primary superficial venous insufficiency: the ascending theory. Observational and hemodynamic data from a 9-year experience. Annals of Vascular Surgery. 2010; 24(6):709-720

23 Biswas S, Clark A, Shields DA. Randomised clinical trial of the duration of compression therapy after varicose vein surgery. European Journal of Vascular and Endovascular Surgery. 2007; 33(5):631-637

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

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

26 Blomgren L, Johansson G, Emanuelsson L, Dahlberg-Akerman A, Thermaenius P, Bergqvist D. Late follow-up of a randomized trial of routine duplex imaging before varicose vein surgery. British Journal of Surgery. 2011; 98(8):1112-1116

27 Bobridge A, Sandison S, Paterson J, Puckridge P, Esplin M. A pilot study of the development and implementation of a 'best practice' patient information booklet for patients with chronic venous insufficiency. Phlebology. 2011; 26(8):338-343

28 Boccalon H, Janbon C, Saumet JL, Tafani A, Roux T, Vilain C. Characteristics of chronic venous insufficiency in 895 patients followed in general practice. International Angiology. 1997; 16(4):226-234

29 Bond R, Whyman MR, Wilkins DC, Walker AJ, Ashley S. A randomised trial of different compression dressings following varicose vein surgery. Phlebology. 1999; 14(1):9-11

30 Bountouroglou DG, Azzam M, Kakkos SK, Pathmarajah M, Young P, Geroulakos G. Ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. European Journal of Endovascular Surgery. 2006; 31(1):93-100

31 Bradshaw C, Pritchett C, Bryce C, Coleman S, Nattress H. Information needs of general day surgery patients. Ambulatory Surgery. 1999; 7(1):39-44

32 Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. American Journal of Preventive Medicine. 1988; 4(2):96-101

33 Brar R, Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. Surgical management of varicose veins: meta-analysis. Vascular. 2010; 18(4):205-220

34 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics. 2002; 21(2):271-292

35 Brethauer SA, Murray JD, Hatter DG, Reeves TR, Hemp JR, Bergan JJ. Treatment of varicose veins: proximal saphenofemoral ligation comparing adjunctive varicose phlebectomy with sclerotherapy at a military medical center. Vascular and Endovascular Surgery. 2001; 35(1):51-58

36 Breu FX, Guggenbichler S, Wollmann JC. 2nd European Consensus Meeting on Foam Sclerotherapy 2006, Tegernsee, Germany. Vasa. 2008; 37(Suppl1):1-29

37 Brown JR, Brown AM. Office diagnosis of lower extremity venous insufficiency and treatment with the use of nonprescription support hose. Journal of the American Osteopathic Association. 1992; 92(4):459-468

38 Bush RG, Bush P, Flanagan J, Fritz R, Gueldner T, Koziarski J et al. Factors associated with recurrence of varicose veins after thermal ablation: 3-year results of the REVATA (REcurrent Veins After Thermal Ablation) study. Journal of Vascular Surgery. 2012; 55(1):297

39 Calcagno D, Rossi JA, Ha C. Effect of saphenous vein diameter on closure rate with ClosureFAST radiofrequency catheter. Vascular and Endovascular Surgery. 2009; 43(6):567-570

40 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ (Clinical Research Ed). 2005; 331(7521):897-900

41 Campbell WB, Decaluwe H, Macintyre JB, Thompson JF, Cowan AR. Most patients with varicose veins have fears or concerns about the future, in addition to their presenting symptoms. European Journal of Vascular and Endovascular Surgery. 2006; 31(3):332-334

42 Campbell WB, Halim AS, Aertssen A, Ridler BM, Thompson JF, Niblett PG. The place of duplex scanning for varicose veins and common venous problems. Annals of the Royal College of Surgeons of England. 1996; 78(6):490-493

43 Campbell WB, Niblett PG, Peters AS, Macintyre JB, Sherriff S, Palfreyman S et al. The clinical effectiveness of hand held Doppler examination for diagnosis of reflux in patients with varicose veins. European Journal of Vascular and Endovascular Surgery. 2005; 30(6):664-669

44 Campbell WB, Niblett PG, Ridler BM, Peters AS, Thompson JF. Hand-held Doppler as a screening test in primary varicose veins. British Journal of Surgery. 1997; 84(11):1541-1543

45 Carpentier PH, Widmer MT, Zemp E, Uhl JF, Cornu-Thenard A. Prognostic signification of venous symptoms in the Basel venous study. Phlebology. 2008; 23(5):241

46 Carradice D, Mekako AI, Hatfield J, Chetter IC. Randomized clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. British Journal of Surgery. 2009; 96(4):369-375

47 Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery. 2011; 98(8):1117-1123

48 Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. Randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. British Journal of Surgery. 2011; 98(4):501-510

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

50 Cavezzi A, Labropoulos N, Partsch H, Ricci S, Caggiati A, Myers K et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs--UIP consensus document. Part II. Anatomy. Vasa. 2007; 36(1):62-71

51 Chaar CIO, Hirsch SA, Cwenar MT, Rhee RY, Chaer RA, Abu Hamad G et al. Expanding the role of endovenous laser therapy: results in large diameter saphenous, small saphenous, and anterior accessory veins. Annals of Vascular Surgery. 2011; 25(5):656-661

52 Chant AD, Davies LJ, Pike JM, Sparks MJ. Support stockings in practical management of varicose veins. Phlebology. 1989; 4(3):167-169

53 Chant AD, Jones HO, Weddell JM. Varicose veins: a comparison of surgery and injection-compression sclerotherapy. Lancet. 1972; 2(7788):1188-1191

54 Chant AD, Magnussen P, Kershaw C. Support hose and varicose veins. British Medical Journal (Clinical Research Ed). 1985; 290(6463):204

55 Chi YW, Ali L, Woods TC. Clinical risk factors to predict deep venous thrombosis post endovenous laser ablation of saphenous veins. Vascular Medicine. 2011; 16(3):235-236

56 Ching T, Roake JA. Net-based information on varicose vein treatments: a tangled web. New Zealand Medical Journal. 2010; 123(1323):-15, 2010

57 Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. Journal of Vascular Surgery. 2010; 52(5):1234-1241

58 Christenson JT, Vines L, Gemayel G. Is there a relationship between increased body mass index and primary venous disease severity and concomitant primary deep venous reflux? Journal of Vascular Surgery. 2012; 55(1):306

59 Ciostek P, Michalak J, Noszczyk W. Improvement in deep vein haemodynamics following surgery for varicose veins. European Journal of Vascular and Endovascular Surgery. 2004; 28(5):473-478

60 Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs--UIP consensus document. Part I. Basic principles. Vasa. 2007; 36(1):53-61

61 Corbett R, Prakash V. Groin recurrence after long saphenous surgery: long-term comparison of primary and re-do operations. Phlebology. 2011; 26(6):265

62 Curtis L. Unit costs of health and social care 2011. Canterbury: Personal Social Services Research Unit, University of Kent; 2011. Available from: http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf

63 Cushman M, Callas PW, Denenberg JO, Bovill EG, Criqui MH. Risk factors for peripheral venous disease resemble those for venous thrombosis: the San Diego Population Study. Journal of Thrombosis and Haemostasis. 2010; 8(8):1730-1735

64 Darke SG, Vetrivel S, Foy DM, Smith S, Baker S. A comparison of duplex scanning and continuous wave Doppler in the assessment of primary and uncomplicated varicose veins. European Journal of Vascular and Endovascular Surgery. 1997; 14(6):457-461

65 Darvall KA, Bate GR, Sam RC, Adam DJ, Silverman SH, Bradbury AW. Patients' expectations before and satisfaction after ultrasound guided foam sclerotherapy for varicose veins. European Journal of Vascular and Endovascular Surgery. 2009; 38(5):642-647

66 Darwood RJ, Gough MJ. Endovenous laser treatment for uncomplicated varicose veins. Phlebology. 2009; 24(Suppl.1):50-61

67 Darwood RJ, Theivacumar N, Dellagrammaticas D, Mavor AID, Gough MJ. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. British Journal of Surgery. 2008; 95(3):294-301

68 Davies AH, Steffen C, Cosgrove C, Wilkins DC. Varicose vein surgery: patient satisfaction. Journal of the Royal College of Surgeons of Edinburgh. 1995; 40(5):298-299

69 De Maeseneer M, Pichot O, Cavezzi A, Earnshaw J, van Rij A, Lurie F et al. Duplex ultrasound investigation of the veins of the lower limbs after treatment for varicose veins: UIP consensus document. European Journal of Vascular and Endovascular Surgery. 2011; 42(1):89-102

70 de Medeiros CA. Comparison of endovenous laser therapy vs. conventional stripping of the great saphenous vein: midterm results. Jornal Vascular Brasileiro. 2006; 5(4):277-287

71 de Medeiros CA, Luccas GC. 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. 2005; 31(12):1685-1694

72 de Roos KP, Bruins FG, Neumann HAM. Compression therapy following ambulatory phlebectomy: a prospective study. Phlebologie. 2008; 37(1):3-6

73 de Roos KP, Nieman FH, Neumann HA. Ambulatory phlebectomy versus compression sclerotherapy: results of a randomized controlled trial. Dermatologic Surgery. 2003; 29(3):221-226

74 Defty C, Eardley N, Taylor M, Jones DR, Mason PF. A comparison of the complication rates following unilateral and bilateral varicose vein surgery. European Journal of Vascular and Endovascular Surgery. 2008; 35(6):745-749

75 Dejode LR. Injection-compression treatment of varicose veins. A follow-up study. British Journal of Surgery. 1970; 57(4):285-286

76 DePalma RG, Hart MT, Zanin L, Massarin EH. Physical examination, Doppler ultrasound and colour flow duplex scanning: guides to therapy for primary varicose veins. Phlebology. 1993; 8(1):7-11

77 Department of Health. NHS reference costs 2010-2011: Appendix NSRC4: NHS trust and PCT combined reference cost schedules. 2011. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140 [Last accessed: 22 October 2012]

78 Diamond KR, Hong MS, Shelpman D, Nelson PR. Outcomes and predictors of secondary intervention for chronic venous insufficiency following endovenous radiofrequency ablation. Journal of Vascular Surgery. 2012; 55(1):304

79 Dias, S, Welton, NJ, Sutton, AJ, and Ades, AE. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Sheffield. Decision Support Unit, ScHARR, 2012 Available from: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis.final.08.05.12.pdf

80 Dias, S, Welton, NJ, Sutton, AJ, Caldwell, DM, Lu, G, and Ades, AE. Inconsistency in networks of evidence based on randomised controlled trials. Sheffield. Decision Support Unit, ScHARR, 2012 Available from: http://www.nicedsu.org.uk/TSD4%20Inconsistency.final.08.05.12.pdf

81 Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet. 1996; 347(8997):292-294

82 Dillon MF, Carr CJ, Feeley TM, Tierney S. Impact of the informed consent process on patients' understanding of varicose veins and their treatment. Irish Journal of Medical Science. 2005; 174(3):23-27

83 Dinn E, Henry M. Treatment of venous ulceration by injection sclerotherapy and compression hosiery: a 5-year study. Phlebology. 1992; 7(1):23-26

84 Disselhoff BC, Buskens E, Kelder JC, der Kinderen DJ, Moll FL. Randomised comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2-year results. European Journal of Vascular and Endovascular Surgery. 2009; 37(3):357-363

85 Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. British Journal of Surgery. 2008; 95(10):1232-1238

86 Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Five-year results of a randomized clinical trial comparing endovenous laser ablation with cryostripping for great saphenous varicose veins. British Journal of Surgery. 2011; 98(8):1107-1111

87 Disselhoff BC, der Kinderen DJ, Moll FL. Is there a risk for lymphatic complications after endovenous laser treatment versus cryostripping of the great saphenous vein? A prospective study. Phlebology. 2008; 23(1):10-14

88 Dixon PM. Duplex ultrasound in the pre-operative assessment of varicose veins. Australasian Radiology. 1996; 40(4):416-421

89 Doran FS, White M. A clinical trial designed to discover if the primary treatment of varicose veins should be by Fegan's method or by an operation. British Journal of Surgery. 1975; 62(1):72-76

90 Durkin MT, Turton EP, Wijesinghe LD, Scott DJ, Berridge DC. Long saphenous vein stripping and quality of life: a randomised trial. European Journal of Vascular and Endovascular Surgery. 2001; 21(6):545-549

91 Dzieciuchowicz L, Krasinski Z, Motowidlo K, Gabriel M. The aetiology and influence of age and gender on the development of advanced chronic venous insufficiency in the population of patients of semi-urban county outpatient vascular clinic in Poland. Phlebology. 2011; 26(2):56-61

92 Eidson JL, Atkins MD, Bohannon WT, Marrocco CJ, Buckley CJ, Bush RL. Economic and outcomes-based analysis of the care of symptomatic varicose veins. Journal of Surgical Research. 2011; 168(1):5-8

93 Eifell RKG, Bhattacharya V, Stansby GP. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for long saphenous vein varices. Cochrane Database of Systematic Reviews. 2006;(1):CD005624

94 Einarsson E, Eklof B, Neglen P. Sclerotherapy or surgery as treatment for varicose veins: a prospective randomized study. Phlebology. 1993; 8(1):22-26

95 Engel AF, Davies G, Keeman JN. Preoperative localisation of the saphenopopliteal junction with duplex scanning. European Journal of Vascular Surgery. 1991; 5(5):507-509

96 Eskelinen E, Rasanen P, Alback A, Lepantalo M, Eskelinen A, Peltonen M et al. Effectiveness of superficial venous surgery in terms of quality-adjusted life years and costs. Scandinavian Journal of Surgery. 2009; 98(4):229-233

97 Figueiredo M, Araujo S, Barros N, Miranda F. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. European Journal of Vascular and Endovascular Surgery. 2009; 38(6):758-763

98 Fischer R, Chandler JG, Stenger D, Puhan MA, De Maeseneer MG, Schimmelpfennig L. Patient characteristics and physician-determined variables affecting saphenofemoral reflux recurrence after ligation and stripping of the great saphenous vein. Journal of Vascular Surgery. 2006; 43(1):81

99 Flessenkamper I, Hartmann M, Stenger D, Roll S. Endovenous laser ablation with and without high ligation compared with high ligation and stripping in the treatment of great saphenous varicose veins: initial results of a multicentre randomized controlled trial. Phlebology. 2012; In press

100 Fraser IA, Perry EP, Hatton M, Watkin DF. Prolonged bandaging is not required following sclerotherapy of varicose veins. British Journal of Surgery. 1985; 72(6):488-490

101 Gasparis AP, Labropoulos N, Pefanis D, Leon LR, Psalms SB, Tassiopoulos AK. Progression of chronic venous disease in post-thrombotic limbs is more rapid when compared with primary. Phlebology. 2008; 23(5):237-238

102 Geraghty JC, Anderson JH, Wilson Y, McArdle CS, Anderson JR. A prospective randomised study to determine the efficacy of O-(b- hydroxyethyl)-rutosides and graduated compression hosiery in controlling varicose vein symptoms. Phlebologie. 1989; 2:881-883

103 Gibson KD, Ferris BL, Polissar N, Neradilek B, Pepper D. Endovenous laser treatment of the short saphenous vein: efficacy and complications. Journal of Vascular Surgery. 2007; 45(4):795-803

104 Gohel MS, Barwell JR, Earnshaw JJ, Heather BP, Mitchell DC, Whyman MR et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study): haemodynamic and anatomical changes. British Journal of Surgery. 2005; 92(3):291-297

105 Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ. 2007; 335(7610):83

106 Gohel MS, Epstein DM, Davies AH. Cost-effectiveness of traditional and endovenous treatments for varicose veins. British Journal of Surgery. 2010; 97(12):1815-1823

107 Gonzalez-Zeh R, Armisen R, Barahona S. Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one-year follow-up results. Journal of Vascular Surgery. 2008; 48(4):940-946

108 Goode SD, Kuhan G, Altaf N, Simpson R, Beech A, Richards T et al. Suitability of varicose veins for endovenous treatments. Cardiovascular and Interventional Radiology. 2009; 32(5):988-991

109 Guest M, Smith JJ, Tripuraneni G, Howard A, Madden P, Greenhalgh RM et al. Randomized clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. Phlebology. 2003; 18(3):130-136

110 Haas E, Sicklinger M. Stripping methods in the treatment of long saphenous vein insufficiency: prospective-randomized colour coded duplex-controlled study to compare three procedures. Phlebologie. 2006; 35(5):237-242

111 Hamel-Desnos CM, Guias BJ, Desnos PR, Mesgard A. Foam sclerotherapy of the saphenous veins: randomised controlled trial with or without compression. European Journal of Vascular and Endovascular Surgery. 2010; 39(4):500-507

112 Hartmann K, Klode J, Pfister R, Toussaint M, Weingart I, Waldermann F et al. Recurrent varicose veins: sonography-based re-examination of 210 patients 14 years after ligation and saphenous vein stripping. Vasa. 2006; 35(1):21-26

113 Helmy EKK, ElKashef O, ElBaz W. Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins-a randomized clinical trial. Angiology. 2011; 62(1):49-54

114 Hinchliffe RJ, Ubhi J, Beech A, Ellison J, Braithwaite BD. A prospective randomised controlled trial of VNUS closure versus surgery for the treatment of recurrent long saphenous varicose veins. European Journal of Vascular and Endovascular Surgery. 2006; 31(2):212-218

115 Hingorani AP, Ascher E, Marks N, Shiferson A, Patel N, Gopal K et al. Predictive factors of success following radio-frequency stylet (RFS) ablation of incompetent perforating veins (IPV). Journal of Vascular Surgery. 2009; 50(4):844-848

116 Hobbs JT. The treatment of varicose veins. A random trial of injection-compression therapy versus surgery. British Journal of Surgery. 1968; 55(10):777-780

117 Hobbs JT. Surgery and sclerotherapy in the treatment of varicose veins. A random trial. Archives of Surgery. 1974; 109(6):793-796

118 Houtermans-Auckel JP, van Rossum E, Teijink JA, Dahlmans AA, Eussen EF, Nicolai SP et al. To wear or not to wear compression stockings after varicose vein stripping: a randomised controlled trial. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):387-391

119 Information Centre for Health and Social Care. Finalised Patient Reported Outcome Measures (PROMs) in England, April 2010 to March 2011: Pre- and post-operative data. 2012. Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1582

120 Information Centre for Health and Social Care. Patient Reported Outcome Measures (PROMs): Finalised score comparison 2010-2011. 2012. Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1582 [Last accessed: 23 October 2012]

121 Information Centre for Health and Social Care. Total procedures and interventions 2010-11. 2012. Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=210 [Last accessed: 22 October 2012]

122 Islamoglu F, Ayik MF, Amanvermez D, Durmaz I. A new alternative in treatment of varicose veins: ligation plus foam sclerotherapy. Dermatologic Surgery. 2011; 37(4):470-479

123 Jagtman BA, Tazelaar DJ, de Leeuw J. Compression sclerotherapy of anterolateral thigh primary varicose veins (lateral accessory saphenous varicose veins): a prospective five-year follow-up study. Phlebology. 2003; 18(2):65-69

124 Jakobsen BH. The value of different forms of treatment for varicose veins. British Journal of Surgery. 1979; 66(3):182-184

125 Jones NA, Webb PJ, Rees RI, Kakkar VV. A physiological study of elastic compression stockings in venous disorders of the leg. British Journal of Surgery. 1980; 67(8):569-572

126 Junger M, Galler S, Klyscz T, Steins A, Hahn M. Improvement of cutaneous microangiopathy by compression therapy in chronic venous insufficiency. Phlebology. 1996; 11(Suppl.1):10-13

127 Kakkar VV. A physiological study of elastic compression stockings in venous disorders of the leg. Phlebologie. 1982; 35(1):101-106

128 Kakkos SK, Bountouroglou DG, Azzam M, Kalodiki E, Daskalopoulos M, Geroulakos G. Effectiveness and safety of ultrasound-guided foam sclerotherapy for recurrent varicose veins: immediate results. Journal of Endovascular Therapy. 2006; 13(3):357-364

129 Kalodiki E, Azzam M, Lattimer CR, Shawish E, Zambas N, Geroulakos G. Randomized controlled trial of ultrasound guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: five-year results. Journal of Vascular Surgery. 2011; 53(1 Suppl.):259-260

130 Kalteis M, Berger I, Messie-Werndl S, Pistrich R, Schimetta W, Polz W et al. High ligation combined with stripping and endovenous laser ablation of the great saphenous vein: early results of a randomized controlled study. Journal of Vascular Surgery. 2008; 47(4):822-829

131 Kent PJ, Weston MJ. Duplex scanning may be used selectively in patients with primary varicose veins. Annals of the Royal College of Surgeons of England. 1998; 80(6):388-393

132 Kim HK, Kim HJ, Shim JH, Baek MJ, Sohn YS, Choi YH. Endovenous lasering versus ambulatory phlebectomy of varicose tributaries in conjunction with endovenous laser treatment of the great or small saphenous vein. Annals of Vascular Surgery. 2009; 23(2):207-211

133 Kim HS, Paxton BE. 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. 2006; 17(9):1449-1455

134 Kim J, Richards S, Kent PJ. Clinical examination of varicose veins: a validation study. Annals of the Royal College of Surgeons of England. 2000; 82(3):171-175

135 King T, Coulomb G, Goldman A, Sheen V, Mcwilliams S, Guptan RC. Experience with concomitant ultrasound-guided foam sclerotherapy and endovenous laser treatment in chronic venous disorder and its influence on Health Related Quality of Life: interim analysis of more than 1000 consecutive procedures. International Angiology. 2009; 28(4):289-297

136 Kordowicz A, Ferguson G, Salaman R, Onwudike M. Quality assurance of venous Duplex scans performed by a vascular surgeon. Phlebology. 2010; 25(6):296-311

137 Koroglu M, Eris HN, Aktas AR, Kayan M, Yesildag A, Cetin M et al. Endovenous laser ablation and foam sclerotherapy for varicose veins: does the presence of perforating vein insufficiency affect the treatment outcome? Acta Radiologica. 2011; 52(3):278-284

138 Kostas TI, Ioannou CV, Drygiannakis I, Georgakarakos E, Kounos C, Tsetis D et al. Chronic venous disease progression and modification of predisposing factors. Journal of Vascular Surgery. 2010; 51(4):900-907

139 Krijnen RM, de Boer EM, Ader HJ, Osinga DS, Bruynzeel DP. Compression stockings and rubber floor mats: do they benefit workers with chronic venous insufficiency and a standing profession? Journal of Occupational and Environmental Medicine. 1997; 39(9):889-894

140 Kundu S, Modabber M. Endovenous ablation for the treatment of varicose veins and lower extremity venous insufficiency. Journal of Radiology Nursing. 2011; 30(1):36-42

141 Labropoulos N, Leon M, Volteas N, Nicolaides AN. Acute and long-term effect of elastic stockings in patients with varicose veins. International Angiology. 1994; 13(2):119-123

142 Labropoulos N, Wang ED, Lanier ST, Khan SU. Factors associated with poor healing and recurrence of venous ulceration. Plastic and Reconstructive Surgery. 2012; 129(1):179-186

143 Lattimer CR, Azzam M, Kalodiki E, Shawish E, Trueman P, Geroulakos G. Cost and effectiveness of laser with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency.

Early results of a randomised controlled trial. European Journal of Vascular and Endovascular Surgery. 2012; 43(5):594-600

144 Leu AJ, Yanar A, Geiger M, Franzeck UK, Bollinger A. Microangiopathy in chronic venous insufficiency before and after sclerotherapy and compression treatment: results of a one-year follow-up study. Phlebology. 1993; 8(3):99-106

145 Levi N, Sillesen H, Nielsen TG, Schroeder TV. Preoperative mapping of the saphenous vein: prognostic value on early postoperative results. Panminerva Medica. 1995; 37(1):11-13

146 Liamis A, Prionidis I, Mathai J, Gorton L, Browne T, Panayiotopoulos YP. Long saphenous vein reverse foam sclerotherapy with saphenofemoral junction ligation compared with head and invagination stripping: a prospective randomized trial. Phlebology. 2005; 20(3):149

147 Lippmann HI, Fishman LM, Farrar RH, Bernstein RK, Zybert PA. Edema control in the management of disabling chronic venous insufficiency. Archives of Physical Medicine and Rehabilitation. 1994; 75(4):436-441

148 Liu X, Jia X, Guo W, Xiong J, Zhang H, Liu M et al. Ultrasound-guided foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping: a prospective clinical study. International Angiology. 2011; 30(4):321-326

149 Luebke T, Brunkwall J. Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. Journal of Cardiovascular Surgery. 2008; 49(2):213-233

150 Luebke T, Gawenda M, Heckenkamp J, Brunkwall J. Meta-analysis of endovenous radiofrequency obliteration of the great saphenous vein in primary varicosis. Journal of Endovascular Therapy. 2008; 15(2):213-223

151 Lugli M, Cogo A, Guerzoni S, Petti A, Maleti O. Effects of eccentric compression by a crossed-tape technique after endovenous laser ablation of the great saphenous vein: a randomized study. Phlebology. 2009; 24(4):151-156

152 Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). Journal of Vascular Surgery. 2003; 38(2):207-214

153 Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O et al. Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up. European Journal of Vascular and Endovascular Surgery. 2005; 29(1):67-73

154 Lurie F, Kistner RL. Trends in patient reported outcomes of conservative and surgical treatment of primary chronic venous disease contradict current practices. Annals of Surgery. 2011; 254(2):363-367

155 Mackenzie RK, Brown DA, Allan PL, Bradbury AW, Ruckley CV. A comparison of patients who developed venous leg ulceration before and after their 50th birthday. European Journal of Vascular and Endovascular Surgery. 2003; 26(2):176-178

156 Mackenzie RK, Lee AJ, Paisley A, Burns P, Allan PL, Ruckley CV et al. Patient, operative, and surgeon factors that influence the effect of superficial venous surgery on disease-specific quality of life. Journal of Vascular Surgery. 2002; 36(5):896-902

157 Magnusson MB, Nelzen O, Volkmann R. Leg ulcer recurrence and its risk factors: a duplex ultrasound study before and after vein surgery. European Journal of Vascular and Endovascular Surgery. 2006; 32(4):453-461

158 Makris SA, Karkos CD, Awad S, London NJ. An "all-comers" venous duplex scan policy for patients with lower limb varicose veins attending a one-stop vascular clinic: is it justified? European Journal of Vascular and Endovascular Surgery. 2006; 32(6):718-724

159 Mariani F, Marone EM, Gasbarro V, Bucalossi M, Spelta S, Amsler F et al. Multicenter randomized trial comparing compression with elastic stocking versus bandage after surgery for varicose veins. Journal of Vascular Surgery. 2011; 53(1):115-122

160 Marsh P, Price BA, Holdstock JM, Whiteley MS. One-year outcomes of radiofrequency ablation of incompetent perforator veins using the radiofrequency stylet device. Phlebology. 2010; 25(2):79-84

161 Marston WA, Brabham VW, Mendes R, Berndt D, Weiner M, Keagy B. The importance of deep venous reflux velocity as a determinant of outcome in patients with combined superficial and deep venous reflux treated with endovenous saphenous ablation. Journal of Vascular Surgery. 2008; 48(2):400-406

162 McLafferty RB, Passman MA, Meissner MH, Caprini JA, Wakefield TW, Iafrati MD et al. Defining gender and racial differences for Venous disease: Implications for the differences discovered. Journal of Vascular Surgery. 2009; 49(5 Suppl.1):38S

163 Medical Advisory Secretariat. Endovascular laser therapy for varicose veins an evidence-based analysis. Toronto, Canada. Medical Advisory Secretariat, 2010

164 Meissner MH. What is the medical rationale for the treatment of varicose veins? Phlebology. 2012; 27 Suppl. 1:27-33

165 Mekako AI, Hatfield J, Bryce J, Heng M, Lee D, McCollum P et al. Combined endovenous laser therapy and ambulatory phlebectomy: refinement of a new technique. European Journal of Vascular and Endovascular Surgery. 2006; 32(6):725-729

166 Melrose DG, Knight MT, Simandl E. The stripping of varicose veins: a clinical trial of intermittent compression dressings. British Journal of Surgery. 1979; 66(1):53-55

167 Mercer KG, Scott DJ, Berridge DC. Preoperative duplex imaging is required before all operations for primary varicose veins. British Journal of Surgery. 1998; 85(11):1495-1497

168 Merchant RF, Pichot O. Long-term outcomes of endovenous radiofrequency obliteration of saphenous reflux as a treatment for superficial venous insufficiency. Journal of Vascular Surgery. 2005; 42(3):502-509

169 Michaels JA, Brazier JE, Campbell WB, Macintyre JB, Palfreyman SJ, Ratcliffe J. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins: cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. British Journal of Surgery. 2006; 93(2):175-181

170 Michaels JA, Campbell WB, Brazier JE, Macintyre JB, Palfreyman SJ, Ratcliffe J et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). Health Technology Assessment. 2006; 10(13):1-196

171 Miyazaki K, Nishibe T, Sata F, Murashita T, Kudo FA, Miyazaki YJ et al. Long-term results of treatments for varicose veins due to greater saphenous vein insufficiency. International Angiology. 2005; 24(3):282-286

172 Moore CJ, McLafferty RB, Lentz M, Schneider JR, Roupenian A, Heller J et al. Venous disease and the effects of increasing body mass index: Results from the national venous screening program. Journal of Vascular Surgery. 2011; 53(1):253

173 Mosti G, Mattaliano V, Arleo S, Partsch H. Thigh compression after great saphenous surgery is more effective with high pressure. International Angiology. 2009; 28(4):274-280

174 Mosti G, Partsch H. Compression stockings with a negative pressure gradient have a more pronounced effect on venous pumping function than graduated elastic compression stockings. European Journal of Vascular and Endovascular Surgery. 2011; 42(2):261-266

175 Mota-Capitao L, Menezes JD, Gouveia-Oliveira A. Clinical predictors of the severity of chronic venous insufficiency of the lower limbs: a multivariate analysis. Phlebology. 1995; 10(4):155-159

176 Motykie GD, Caprini JA, Arcelus JI, Reyna JJ, Overom E, Mokhtee D. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. Dermatologic Surgery. 1999; 25(2):116-120

177 Mouton WG, Bergner M, Zehnder T, von Wattenwyl R, Naef M, Wagner HE. Recurrence after surgery for varices in the groin is not dependent on body mass index. Swiss Medical Weekly. 2008; 138(11-12):186-188

178 Murad MH, Coto-Yglesias F, Zumaeta-Garcia M, Elamin MB, Duggirala MK, Erwin PJ et al. A systematic review and meta-analysis of the treatments of varicose veins. Journal of Vascular Surgery. 2011; 53(5 Suppl.):49S-65S

179 Murphy MA, Joyce WP. Information for surgical patients: implications of the World Wide Web. European Journal of Surgery. 2001; 167(10):728-733

180 Myers KA, Jolley D, Clough A, Kirwan J. Outcome of ultrasound-guided sclerotherapy for varicose veins: medium-term results assessed by ultrasound surveillance. European Journal of Vascular and Endovascular Surgery. 2007; 33(1):116-121

181 Nash TP. Venous ulceration: factors influencing recurrence after standard surgical procedures. Medical Journal of Australia. 1991; 154(1):48-50

182 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London. NICE, 2008 Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

183 Nelzen O. Varicose vein recurrence and patient satisfaction 10-15 years following saphenous and perforator surgery. Phlebology. 2010; 25(6):309

184 Nesbitt C, Eifell RKG, Coyne P, Badri H, Bhattacharya V, Stansby G. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for great saphenous vein varices. Cochrane Database of Systematic Reviews. 2011;(10):CD005624

185 Netherlands Organisation for Health Research and Development (ZonMw). FOAM-study. Cost minimization study comparing surgery versus duplex guided foam sclerotherapy of varicose veins: a randomized controlled study. 2005.

186 NHS Business Services Authority. NHS electronic drug tariff. 2011. Available from: http://www.ppa.org.uk/edt/August_2011/mindex.htm [Last accessed: 25 October 2011]

187 NHS Supply Chain. NHS Supply Chain catalogue. 2012. Available from: http://www.supplychain.nhs.uk/ [Last accessed: 13 December 2012]

188 Nicolini P. Treatment of primary varicose veins by endovenous obliteration with the VNUS closure system: results of a prospective multicentre study. European Journal of Vascular and Endovascular Surgery. 2005; 29(4):433-439

189 Nordon IM, Hinchliffe RJ, Brar R, Moxey P, Black SA, Thompson MM et al. A prospective double-blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins. Annals of Surgery. 2011; 254(6):876-881

190 O'Hare JL, Stephens J, Parkin D, Earnshaw JJ. Randomized clinical trial of different bandage regimens after foam sclerotherapy for varicose veins. British Journal of Surgery. 2010; 97(5):650-656

191 Office for National Statistics. England and Wales, Interim Life Tables, 1980-82 to 2008-10. 2011. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-223324 [Last accessed: 22 October 2012]

192 Oguzkurt L, Ozkan U, Demirturk O, Gur S, Tercan F. Symptomatic improvement after endovenous laser ablation of the saphenous vein insufficiency: experience of a single center in 485 patients. Cardiovascular and Interventional Radiology. 2010; 33:309

193 Oinonen A, Lehtola A, Sugano N, Alback A, Lepantalo M. Communicating Doppler-derived information in superficial venous surgery. Phlebology. 2007; 22(3):137-141

194 Olivencia JA. A study of the competency of the saphenopopliteal junction by duplex ultrasonography. Dermatologic Surgery. 1998; 24(4):443-444

195 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2012. Available from: http://www.oecd.org/std/ppp [Last accessed: 7 June 2012]

196 Ozsvath KJ, Saltzberg S, Taggert JB, Chang BB, Kreienberg PB, Mehta M et al. Venous ablation can be performed safely on high-risk patients. Journal of Vascular Surgery. 2010; 52(3):804

197 Pachler J, Baekgard N, Panduro JL, Krogh CJ, Sillesen H. Pre-operative duplex scanning of the popliteal fossa may improve the results of saphenopopliteal ligation. Journal of Vascular Investigation. 1998; 4(4):157-160

198 Paisley AM, Bradbury AW. Comparison of the effect of primary and recurrent varicose vein surgery on symptoms and quality of life. British Journal of Surgery. 2000; 87(4):501

199 Palfreyman SJ, Drewery-Carter K, Rigby K, Michaels JA, Tod AM. Varicose veins: a qualitative study to explore expectations and reasons for seeking treatment. Journal of Clinical Nursing. 2004; 13(3):332-340

200 Palfreyman SJ, Michaels JA. A systematic review of compression hosiery for uncomplicated varicose veins. Phlebology. 2009; 24 Suppl.1:13-33

201 Pannier F, Hoffmann B, Stang A, Jockel K-H, Rabe E. Prevalence and acceptance of therapy with medical compression stockings: results of the Bonn Vein Study. Phlebologie. 2007; 36(5):245-249

202 Pannier F, Rabe E. Progression of chronic venous disorders: results from the Bonn Vein Study. Journal of Vascular Surgery. 2011; 53(1):254-255

203 Pannier F, Rabe E. The relevance of the natural history of varicose veins and refunded care. Phlebology. 2012; 27 Suppl. 1:23-26

204 Perala J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T et al. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. Annals of Vascular Surgery. 2005; 19(5):669-672

205 Phillips GWL, Paige J, Molan MP. A comparison of colour duplex ultrasound with venography and varicography in the assessment of varicose veins. Clinical Radiology. 1995; 50(1):20-25

206 Piachaud D, Weddell JM. Cost of treating varicose veins. Lancet. 1972; 2(788):1191-1192

207 Piachaud D, Weddell JM. The economics of treating varicose veins. International Journal of Epidemiology. 1972; 1(3):287-294

208 Pichot O, Sessa C, Chandler JG, Nuta M, Perrin M. Role of duplex imaging in endovenous obliteration for primary venous insufficiency. Journal of Endovascular Therapy. 2000; 7(6):451-459

209 Pierik EGJM, Toonder IM, van Urk H, Wittens CHA. Validation of duplex ultrasonography in detecting competent and incompetent perforating veins in patients with venous ulceration of the lower leg. Journal of Vascular Surgery. 1997; 26(1):49-52

210 Pittaluga P, Chastanet S. Lymphatic complications after varicose veins surgery: risk factors and how to avoid them. Phlebology. 2012; 27 Suppl. 1:139-142

211 Pittaluga P, Chastanet S, Rea B, Barbe R. Midterm results of the surgical treatment of varices by phlebectomy with conservation of a refluxing saphenous vein. Journal of Vascular Surgery. 2009; 50(1):107-118

212 Pleass HCC, Holdsworth JD. Audit of introduction of hand-held Doppler and duplex ultrasound in the management of varicose veins. Annals of the Royal College of Surgeons of England. 1996; 78(6):494-496

213 Pronk P, Gauw SA, Mooij MC, Gaastra MT, Lawson JA, van Goethem AR et al. Randomised controlled trial comparing sapheno-femoral ligation and stripping of the great saphenous vein with endovenous laser ablation (980 nm) using local tumescent anaesthesia: one year results. European Journal of Vascular and Endovascular Surgery. 2010; 40(5):649-656

214 Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P. Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. Journal of Vascular Surgery. 2005; 42(3):488-493

215 Puggioni A, Marks N, Hingorani A, Shiferson A, Alhalbouni S, Ascher E. The safety of radiofrequency ablation of the great saphenous vein in patients with previous venous thrombosis. Journal of Vascular Surgery. 2009; 49(5):1248-1255

216 Rabe E. Epidemiology of varicose veins. Phlebolymphology. 2010; 17(1):21

217 Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. Annals of Vascular Surgery. 2007; 21(6):790-795

218 Raraty MGT, Greaney MG, Blair SD. There is no benefit from 6 weeks' postoperative compression after varicose vein surgery: a prospective randomised trial. Phlebology. 1999; 14(1):21-25

219 Rasmussen LH, Bjoern L, Lawaetz M, Blemings A, Lawaetz B, Eklof B. 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. 2007; 46(2):308-315

220 Rasmussen LH, Bjoern L, Lawaetz M, Lawaetz B, Blemings A, Eklof B. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. European Journal of Vascular and Endovascular Surgery. 2010; 39(5):630-635

221 Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. British Journal of Surgery. 2011; 98(8):1079-1087

222 Rass K, Frings N, Glowacki P, Hamsch C, Graber S, Vogt T et al. Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein: two-year results of a randomized clinical trial (RELACS Study). Archives of Dermatology. 2012; 148(1):49-58

223 Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, Macintyre JB, Michaels JA. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. British Journal of Surgery. 2006; 93(2):182-186

224 Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H et al. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. Journal of Vascular Surgery. 2002; 35(5):958-965

225 Rautio T, Perala J, Biancari F, Wiik H, Ohtonen P, Haukipuro K et al. Accuracy of hand-held Doppler in planning the operation for primary varicose veins. European Journal of Vascular and Endovascular Surgery. 2002; 24(5):450-455

226 Rautio T, Perala J, Wiik H, Haukipuro K, Juvonen T. Influence of preoperative duplex ultrasonography on the operative procedure for primary varicose vein surgery. Phlebology. 2002; 16(4):149-153

227 Rhodes DJ, Hadfield GJ. Treatment of varicose veins by injection and compression. Practitioner. 1972; 208(248):809-817

228 Rigby KA, Palfreyman SJ, Beverley C, Michaels JA. Surgery versus sclerotherapy for the treatment of varicose veins. Cochrane Database of Systematic Reviews. 2004;(4):CD004980

229 Robertson LA, Boghossian S, Evans CJ, Lee AJ, Allan PL, Ruckley V et al. Incidence and risk factors for development of varicose veins in the general population: Edinburgh Vein Study. Journal of Vascular Surgery. 2011; 53(1):254

230 Robertson LA, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH et al. Risk factors for chronic ulceration in patients with varicose veins: a case control study. Journal of Vascular Surgery. 2009; 49(6):1490-1498

231 Rodrigus I, Bleyn J. For how long do we have to advise elastic support after varicose vein surgery? A prospective randomized study. Phlebology. 1991; 6(2):95-98

232 Rutgers PH, Kitslaar PJ. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. American Journal of Surgery. 1994; 168(4):311-315

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

234 Safar H, Shawa N, Al-Ali J, Al-Nassar M, Dashti H, Asfar S. Is there a need for Doppler vascular examination for the diagnosis of varicose vein? A prospective study. Medical Principles and Practice. 2004; 13(1):43-46

235 Sains PS, Reddy KM, Jones HJS, Derodra JK. Audit of varicose vein surgery: the patients' perspective. Phlebology. 2005; 20(4):179-182

236 Salaman RA, Fligelstone LJ, Pugh KG, Harding KG. Hand-held bi-directional Doppler versus colour duplex scanning in the pre-operative assessment of varicose veins. Journal of Vascular Investigation. 1995; 4(1):183-186

237 Sarvananthan T, epherd AC, llenberg T, vies AH. Neurological complications of sclerotherapy for varicose veins. Journal of Vascular Surgery. 2012; 55(1):243-251

238 Schanzer H. Endovenous ablation plus microphlebectomy/sclerotherapy for the treatment of varicose veins: single or two-stage procedure? Vascular and Endovascular Surgery. 2010; 44(7):545-549

239 School of Health and Related Research. Clinical and cost-effectiveness of methods of managing varicose veins. 2012. Available from: http://www.hta.ac.uk/2523 [Last accessed: 13 December 2012]

240 Schul MW, Eaton T, Erdman B. Compression versus sclerotherapy for patients with isolated refluxing reticular veins and telangiectasia: a randomized trial comparing quality-of-life outcomes. Phlebology. 2011; 26(4):148-156

241 Schultheiss R, Billeter M, Bollinger A, Franzeck UK. Comparison between clinical examination, cw-Doppler ultrasound and colour-duplex sonography in the diagnosis of incompetent perforating veins. European Journal of Vascular and Endovascular Surgery. 1997; 13(2):122-126

242 Scott TE, LaMorte WW, Gorin DR, Menzoian JO. Risk factors for chronic venous insufficiency: a dual case-control study. Journal of Vascular Surgery. 1995; 22(5):622-628

243 Scurr JRH. www.Accurate information for varicose vein patients.com? Annals of the Royal College of Surgeons of England. 2008; 90(7):554-556

244 Shadid N, Ceulen R, Nelemans P, Dirksen C, Veraart J, Schurink GW et al. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. British Journal of Surgery. 2012; 99(8):1062-1070

245 Shepherd AC, Gohel MS, Brown LC, Metcalfe MJ, Hamish M, Davies AH. Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins. British Journal of Surgery. 2010; 97(6):810-818

246 Shepherd AC, Gohel MS, Lim CS, Hamish M, Davies AH. Factors affecting post operative pain following endovenous ablation of varicose veins. Journal of Vascular Surgery. 2009; 49(5 Suppl. 1):39S

247 Shepherd AC, Gohel MS, Lim CS, Hamish M, Davies AH. The treatment of varicose veins: an investigation of patient preferences and expectations. Phlebology. 2010; 25(2):54-65

248 Shingler S, Robertson L, Boghossian S, Stewart M. Compression stockings for the initial treatment of varicose veins in patients without venous ulceration. Cochrane Database of Systematic Reviews. 2011; 11:CD008819

249 Shouler PJ, Runchman PC. Varicose veins: optimum compression after surgery and sclerotherapy. Annals of the Royal College of Surgeons of England. 1989; 71(6):402-404

250 Singh S, Lees TA, Donlon M, Harris N, Beard JD. Improving the preoperative assessment of varicose veins. British Journal of Surgery. 1997; 84(6):801-802

251 Smith JJ, Brown L, Greenhalgh RM, Davies AH. Randomised trial of pre-operative colour duplex marking in primary varicose vein surgery: outcome is not improved. European Journal of Vascular and Endovascular Surgery. 2002; 23(4):336-343

252 Solis JV, Ribe L, Portero JL, Rio J. Stripping saphenectomy, CHIVA and laser ablation for the treatment of the saphenous vein insufficiency. Ambulatory Surgery. 2009; 15(1):11-14

253 Somjen GM, Donlan J, Hurse J, Bartholomew J, Weir E, Johnston AH et al. Duplex ultrasound examination of the acutely painful and swollen leg. Dermatologic Surgery. 1996; 22(4):383-387

254 Srilekha A, Karunanithy N, Corbett CRR. Informed consent: what do we tell patients about the risk of fatal pulmonary embolism after varicose vein surgery? Phlebology. 2005; 20(4):175-178

255 Stother IG, Bryson A, Alexander S. The treatment of varicose veins by compression sclerotherapy. British Journal of Surgery. 1974; 61(5):387-390

256 Stotter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping, and cryostripping in the treatment of great saphenous vein insufficiency. Phlebology. 2006; 21(2):60-64

257 Subramonia S, Lees T. Radiofrequency ablation vs conventional surgery for varicose veins: a comparison of treatment costs in a randomised trial. European Journal of Vascular and Endovascular Surgery. 2010; 39(1):104-111

258 Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. British Journal of Surgery. 2010; 97(3):328-336

259 Tellings SS, Ceulen RP, Sommer A. Surgery and endovenous techniques for the treatment of small saphenous varicose veins: a review of the literature. Phlebology. 2011; 26(5):179-184

260 Thaler E, Huch R, Huch A, Zimmermann R. Compression stockings prophylaxis of emergent varicose veins in pregnancy: a prospective randomised controlled study. Swiss Medical Weekly. 2001; 131(45-46):659-662

261 Theivacumar NS, Darwood R, Gough MJ. Neovascularisation and recurrence 2 years after varicose vein treatment for sapheno-femoral and great saphenous vein reflux: a comparison of

surgery and endovenous laser ablation. European Journal of Vascular and Endovascular Surgery. 2009; 38(2):203-207

262 Theivacumar NS, Darwood RJ, Dellegrammaticas D, Mavor AID, Gough MJ. The clinical significance of below-knee great saphenous vein reflux following endovenous laser ablation of above-knee great saphenous vein. Phlebology. 2009; 24(1):17-20

263 Theivacumar NS, Darwood RJ, Gough MJ. Endovenous laser ablation (EVLA) of the anterior accessory great saphenous vein (AAGSV): abolition of sapheno-femoral reflux with preservation of the great saphenous vein. European Journal of Vascular and Endovascular Surgery. 2009; 37(4):477-481

264 Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AI, Gough MJ. The clinical significance of persistent below-knee great saphenous vein (BK-GSV) reflux following endovenous GSV laser ablation (EVLA): do we need to modify treatment? Phlebology. 2006; 23(1):141-156

265 Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AID, Gough MJ. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. British Journal of Surgery. 2007; 94(6):722-725

266 Theivacumar NS, Dellagrammaticas D, Darwood RJ, Mavor AID, Gough MJ. Fate of the great saphenous vein following endovenous laser ablation: does re-canalisation mean recurrence? European Journal of Vascular and Endovascular Surgery. 2008; 36(2):211-215

267 Theivacumar NS, Dellagrammaticas D, Mavor AID, Gough MJ. Endovenous laser ablation: does standard above-knee great saphenous vein ablation provide optimum results in patients with both above- and below-knee reflux? A randomized controlled trial. Journal of Vascular Surgery. 2008; 48(1):173-178

268 Thomasset SC, Butt Z, Liptrot S, Fairbrother BJ, Makhdoomi KR. Ultrasound guided foam sclerotherapy: Factors associated with outcomes and complications. European Journal of Vascular and Endovascular Surgery. 2010; 40(3):389-392

269 Tisi PV. Varicose veins. Clinical Evidence. 2011; 2011:1-22

270 Travers JP, Makin GS. Reduction of varicose vein recurrence by use of postoperative compression stockings. Phlebology. 1994; 9(3):104-107

271 Treiman GS, Copland S, McNamara RM, Yellin AE, Schneider PA, Treiman RL. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. Journal of Vascular Surgery. 2001; 33(6):1158-1164

272 Tretbar LL, Pattisson PH. Injection-compression treatment of varicose veins. American Journal of Surgery. 1970; 120(4):539-541

273 Tzilinis A, Salles-Cunha SX, Dosick SM, Gale SS, Seiwert AJ, Comerota AJ. Chronic venous insufficiency due to great saphenous vein incompetence treated with radiofrequency ablation: an effective and safe procedure in the elderly. Vascular and Endovascular Surgery. 2005; 39(4):341-345

274 Uhl JF, Cornu-Thenard A, Carpentier PH, Widmer MT, Partsch H, Antignani PL. Clinical and hemodynamic significance of corona phlebectatica in chronic venous disorders. Journal of Vascular Surgery. 2005; 42(6):1163-1168

275 van den Bos R, Kockaert M, Neumann N, Nijsten T. New endovenous therapies of lower extremity varicosities are at least as effective as surgical stripping and sclerotherapy: meta-analysis and meta-regression of case series and randomized clinical trials. Phlebology. 2008; 23(Suppl.1)

276 Van der heiden FH, Bruyninckx C. Pre-operative colour coded duplexin varicose veins of the lower extremity. European Journal of Surgery. 1993; 159:329-333

277 van Neer P, Veraart JCJM, Neumann H. Posterolateral thigh perforator varicosities in 12 patients: a normal deep venous system and successful treatment with ultrasound-guided sclerotherapy. Dermatologic Surgery. 2006; 32(11):1346-2

278 Vandy F, Blackburn S, Bloom J, Clay A, Fellows E, Guire K et al. Performing complete superficial vein ablation in patients with obesity and severe chronic venous disease: who benefits? Journal of Vascular Surgery. 2011; 53(6 Suppl. 1):13S

279 Vuylsteke M, Van den Bussche D, Audenaert EA, Lissens P. Endovenous laser obliteration for the treatment of primary varicose veins. Phlebology. 2006; 21(2):80-87

280 Ward AL, Braithwaite BD. Most patients agree that an online Aberdeen Varicose Vein Questionnaire is useful for rationing surgical treatment. Phlebology. 2011; 26(6):264

281 Weiss RA, Sadick NS, Goldman MP, Weiss MA. Post-sclerotherapy compression: controlled comparative study of duration of compression and its effects on clinical outcome. Dermatologic Surgery. 1999; 25(2):105-108

282 Weiss RA, Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radiofrequency catheter under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. Dermatologic Surgery. 2002; 28(1):38-42

283 Welch HJ. Endovenous ablation of the great saphenous vein may avert phlebectomy for branch varicose veins. Journal of Vascular Surgery. 2006; 44(3):601-605

284 Wills V, Moylan D, Chambers J. The use of routine duplex scanning in the assessment of varicose veins. Australian and New Zealand Journal of Surgery. 1998; 68(1):41-44

285 Wright AP, Berridge DC, Scott DJA. Return to work following varicose vein surgery: influence of type of operation, employment and social status. European Journal of Vascular and Endovascular Surgery. 2006; 31(5):553-557

286 Wright D, Gobin JP, Bradbury AW, Coleridge-Smith P, Spoelstra H, Berridge D et al. Varisolve 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. 2006; 21(4):180-190

287 Xenos E, Bietz G, Minion D, Abedi N, Sorial E, Karagiorgos N et al. Endoluminal thermal ablation versus stripping of the saphenous vein: meta-analysis of recurrence of reflux. International Journal of Angiology. 2009; 18(2):75-78

288 Yamaki T, Sasaki K, Nozaki M. Preoperative duplex-derived parameters and angioscopic evidence of valvular incompetence associated with superficial venous insufficiency. Journal of Endovascular Therapy. 2002; 9(2):229-233

289 Zamboni P, Gianesini S, Menegatti E, Tacconi G, Palazzo A, Liboni A. Great saphenous varicose vein surgery without saphenofemoral junction disconnection. British Journal of Surgery. 2010; 97(6):820-825

290 Zubilewicz R, Chmiel-Perzynska I, Derkacz M, Schabowski J. The women's span of knowledge about chronic venous disease. Family Medicine and Primary Care Review. 2009; 11(4):919-922