Diagnose en behandeling van spataders in de benen

KCE reports 164A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Titel: Diagnose en behandeling van spataders in de benen

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VOORWOORD

Wanneer nieuwe medische technieken of nieuwe behandelingen hun intrede doen, stelt zich telkens de vraag of men hieraan de voorkeur moet geven in plaats van aan de oude en of men de facturatiecodes moet aanpassen om rekening te houden met het verschil in kostprijs tussen de oude en de nieuwe technieken.

Dit soort vragen stelde zich sinds enige tijd ook voor de diagnose en behandeling van spataders (varices). De heelkundige 'stripping', die jarenlang het monopolie had op het vlak van chirurgische behandeling, moet geleidelijk plaats ruimen voor minder invasieve technieken, die daardoor aantrekkelijker zijn zowel voor de arts als voor de patiënt.

Maar zijn deze nieuwe technieken even doeltreffend als de oude? Hebben ze geen ernstige bijwerkingen? Zetten ze de gebruikelijke aanpak op het vlak van anesthesie op losse schroeven? Kortom, moeten we de organisatie van de behandeling van spataders nu volledig herzien?

Aangezien het om een pathologie gaat die zeer veel voorkomt, is het logisch dat de beleidsinstanties, en met name het RIZIV, hierin klaarheid willen scheppen. Daarom werd het KCE gevraagd om deze problematiek nader te bekijken.

De uitdaging van dit project bestond erin voldoende homogene gegevens uit de literatuur te halen met betrekking tot een aantal uiteenlopende procedures, die bovendien nog in volle evolutie zijn. De bundeling van de bevindingen uit de wetenschappelijk literatuur gebeurde met de medewerking van Abacus International®. En dank zij de ondersteuning van een aantal clinici kon het onderzoek specifiek worden toegespitst op de technieken die momenteel in België worden gebruikt. Wij willen hen hiervoor ten zeerste bedanken.

Jean Pierre CLOSON
Adjunct Algemeen Directeur

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Algemeen Directeur

Samenvatting

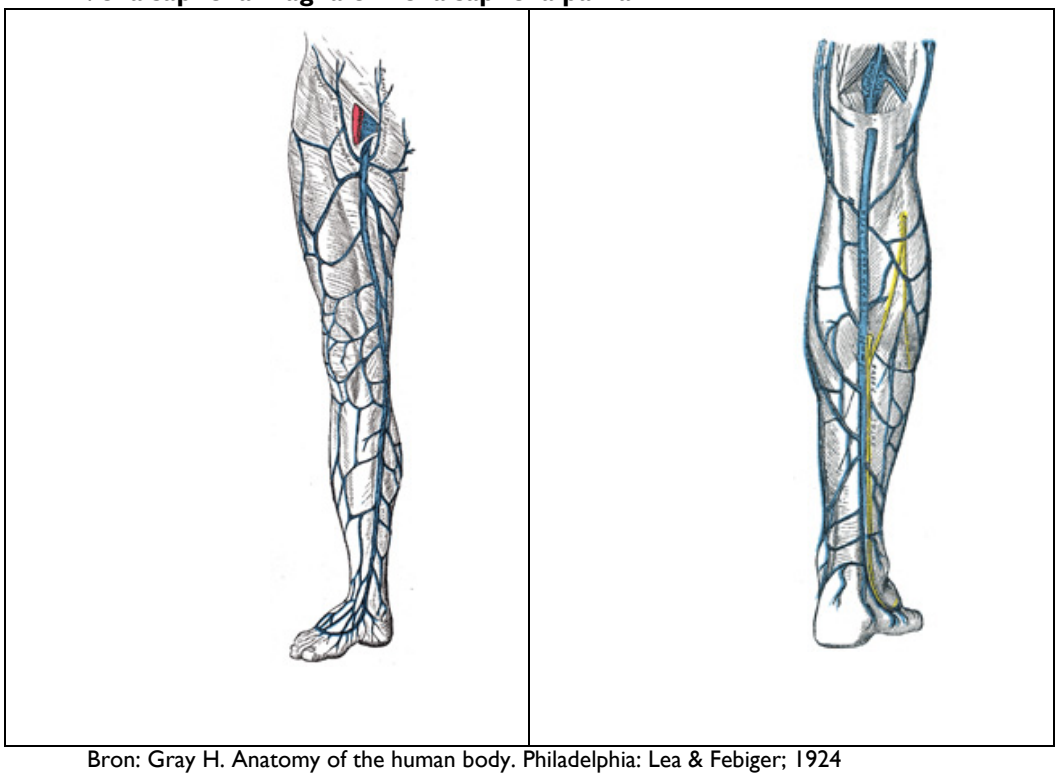
INLEIDING

SPATADERS IN DE BENEN

Spataders in de benen zijn aders die permanent uitgezet zijn, tijdens het rechtopstaan en een diameter van minstens 3 mm hebben. De clinici delen ze in volgens de "CEAP"-classificatie (Clinical severity – Etiology - Anatomy - Pathophysiology). De klinische ernst ("C") wordt geëvalueerd volgens 6 stadia: van het stadium C1 (teleangiëctasieën) tot stadium C6 (actief veneus ulcus).

De voornaamste symptomen zijn tintelingen, jeuk, pijn, vermoeidheid, een zwaar gevoel in de benen en dit vooral wanneer men langdurig moet rechtstaan. De klinische symptomen zijn onder meer oedeem en het zichtbaar worden van de aders die uitgezet zijn en kronkelend onder de huid liggen. Zweren (ulcera) en tromboflebitis zijn mogelijke complicaties.

Vena saphena magna en vena saphena parva



Bron: Gray H. Anatomy of the human body. Philadelphia: Lea & Febiger; 1924

WELKE DIAGNOSTISCHE PROCEDURES ZIJN BESCHIKBAAR?

In België werden in 2010 praktijkrichtlijnen opgesteld door het Consilium Radiologicum. In overeenstemming met een eerdere internationale consensus (2006) beveelt deze gids het gebruik aan van kleuren-echodoppler (« *doppler-ultrasound* ») voor het op punt stellen van de diagnose van de meeste gevallen van spataders (varices). Andere onderzoeken (magnetische resonantie, tomografie, flebografie) kunnen worden voorgesteld in uitzonderlijke gevallen (waaronder aangeboren afwijkingen).

WELKE BEHANDELINGEN WORDEN MOMENTEEL VOORGESTELD?

De huidig voorgestelde behandelingen omvatten maatregelen zoals gewichtsverlies, het vermijden van langdurig rechtstaan, het hoger leggen van de benen, lichaamsoefeningen, compressie (therapeutische elastische kousen, elastische verbanden) en medicatie.

Daarnaast kan ook een klassieke heelkundige ingreep of een van de meer recente endoveneuze technieken (laser, radiofrequentie, sclerotherapie) worden overwogen. Deze laatste technieken worden hetzij alleen uitgevoerd, hetzij in combinatie met heelkunde.

Klassieke heelkundige aanpak

Bij klassieke chirurgie (ook "stripping" genaamd) combineert men het afbinden van de verbinding tussen de vena saphena magna en de vena femoralis of tussen de vena saphena parva en de vena poplitea met het verwijderen van de stam van de vena saphena en van bijhorende insufficiënte oppervlakkige venen. Er bestaan verschillende varianten van deze techniek.

Thermische ablatie door endoveneuze laserbehandeling

Een dunne optische vezel wordt in de te behandelen ader gebracht: de energie van de lichtstraal vernietigt de wand van de ader en veroorzaakt zo een afsluiting van de ader.

Thermische ablatie door radiofrequentie

Net zoals bij de vorige techniek wordt een katheter in de ader gebracht waarbij gebruik wordt gemaakt van de eigenschappen van elektromagnetische stroom om verhitting te veroorzaken, met een zelfde effect als bij laserbehandeling.

Sclerotherapie met schuim of vloeistof via een endoveneuze katheter

De inspuiting van een scleroserend middel in de ader veroorzaakt een ontstekingsreactie die tot occlusie leidt. Tegenwoordig wordt de scleroserende vloeistof meestal vervangen door een schuimvormige emulsie ("foam sclerotherapy ").

KADER VAN HET ONDERZOEK

De diagnose en behandeling van spataders in de benen is de laatste jaren sterk geëvolueerd. Voor het in beeld brengen van spataders in de onderste ledematen heeft de kleuren-echodoppler de eerder genoemde onderzoeken (zoals volumetrie, flebografie) haast volledig verdrongen. De eerste krachtlijn van dit onderzoek buigt zich dan ook over de vraag of het aangewezen is eventuele bijkomende onderzoeken te laten uitvoeren (zoals magnetische resonantie).

Wat betreft de behandeling van spataders in de benen, is de terugbetaling van de ingrepen momenteel gebaseerd op de klassieke chirurgische technieken. In de praktijk stelt men nochtans een toenemend gebruik vast van de hierboven beschreven nieuwe technieken. Hierbij stelt zich de vraag van hun doeltreffendheid en veiligheid, maar ook welk type anesthesie het best geschikt is om in deze omstandigheden te gebruiken.

ONDERZOEKSVRAGEN

Dit systematisch literatuuronderzoek analyseert drie onderzoeksvragen:

- Wat is de waarde van de verschillende diagnostische procedures voor de bevestiging van de klinische diagnose en om richting te geven aan de behandeling van spataders in de onderste ledematen.
- Wat is de klinische doeltreffendheid en de veiligheid van de op dit moment beschikbare behandeltechnieken?
- Bestaan er gegevens met betrekking tot de meest geschikte technieken voor anesthesie al naargelang het type behandeling?

De studiepopulatie omvatte patiënten met klinische tekenen van spataders in de benen, met uitzondering van zwangere vrouwen, patiënten die alleen teleangiëctasieën vertoonden (klinisch stadium C1) of personen die andere veneuze pathologieën vertoonden (zoal tromboflebitis). De behandeling van complicaties werd eveneens uit deze studie uitgesloten. De vraag vanaf welk klinisch stadium een ingreep aangewezen is, valt buiten het kader van deze studie.

De doeltreffendheid van een behandeling wordt afgemeten aan het al dan niet terugkeren van de symptomen of van de spataders (en hun klinisch stadium), het verschijnen van complicaties, de levenskwaliteit. De studies meten tevens meestal het percentage 'repermeabilisatie' of occlusie tijdens de opvolging (wordt gemeten via echodoppler), maar de correlatie van deze gegevens met de klinische symptomen is moeilijk te interpreteren.

METHODEN

Het literatuuronderzoek gebeurde in Medline, EMBASE en de Cochrane Library. Voor de diagnostische procedures raadpleegden de onderzoekers ook nog de Medion-databank, en voor de behandelingen de website van het International Network of Agencies for Health Technology Assessment (INAHTA) en dat van de lopende klinische onderzoeken (clinicaltrials.gov) .

De selectie van de publicaties, de evaluatie van hun kwaliteit, het opstellen van de tabellen van bewijskracht en de toekenning van een kwaliteitsniveau gebeurden volgens de procedures van het KCE.

RESULTATEN

GESELECTEERDE STUDIES

Twee diagnostische studies

Voor de diagnostische studies leverde de zoekstrategie 1854 referenties op (review artikels, gerandomiseerde gecontroleerde studies en observationele studies). Bijna de helft van de referenties werd in meer dan één bibliografische databank teruggevonden (n=817). Een eerste selectieronde (op titel en abstract) leidde tot het uitsluiten van de overgrote meerderheid van de studies, voornamelijk op basis van:

- de populatie (andere veneuze pathologieën, behandeling van complicaties: n=738);
- andere onderzoekstechnieken dan deze die initieel geselecteerd werden op basis van hun potentiële klinische relevantie (echodoppler, flebografie, pre-operatieve arteriële doppler, magnetische resonantie, intravasculaire echografie: n = 210);

Van de 18 in eerste instantie weerhouden studies werden er na volledige tekstanalyse nogmaals 16 uitgesloten: voornamelijk omwille van het feit dat ze de waarde van de handdoppler ("hand-held Doppler") analyseerden, een techniek die in de huidige Belgische praktijk als achterhaald wordt beschouwd. Uiteindelijk werden twee studies weerhouden.

Therapeutische studies

Een eerste zoektocht naar review artikels identificeerde 740 publicaties: 22 werden weerhouden na evaluatie van hun kwaliteit. Voor wat betreft de gerandomiseerde gecontroleerde klinische studies (RCT's) werden 1914 referenties geïdentificeerd: 15 RCT's met gering risico op bias werden uiteindelijk geselecteerd. De meeste uitsluitingen hadden betrekking op publicaties die in meerdere databanken voorkwamen, of met populaties die niet overeenstemden met die gedefinieerd in de hierboven vermelde inclusiecriteria (spataders in de onderste ledematen zonder andere veneuze pathologieën).

De analyse van de bijwerkingen van de klassieke chirurgie en van de endoveneuze technieken is gebaseerd op de bijwerkingen die vermeld werden in de therapeutische studies: ze werd aangevuld door niet gerandomiseerde studies die deze bijwerkingen onderzochten.

Een aanvullend literatuuronderzoek met betrekking tot anesthesietechnieken leverde geen enkele studie op die niet al opgenomen was in de hierboven vermelde onderzoeken. De resultaten zijn gebaseerd op de informatie die beschikbaar was in de therapeutische studies en vooral op een Canadese health technology assessment die specifiek over dit onderwerp ging.

BEVESTIGING VAN DE ROL VAN DE ECHODOPPLER VOOR DE PRE-OPERATIEVE DIAGNOSE

De twee geselecteerde studies beschouwen de echodoppler als het referentieonderzoek. De eerste studie (343 gevallen) vergelijkt patiënten die geopereerd werden na het uitvoeren van dit onderzoek met patiënten die uitsluitend op klinische gegevens werden geopereerd. Het percentage recidieven en herinterventies na twee jaar is aanzienlijk hoger bij patiënten die uitsluitend geopereerd werden op basis van een klinisch onderzoek in vergelijking met de groep met echodoppler (14 versus 2 gevallen). Op het ogenblik van het verschijnen van dit rapport bevestigt de publicatie van meer recente resultaten, met een opvolgingsperiode van 7 jaar, het voordeel van de echodoppler.

De tweede geselecteerde studie besloot dat, hoewel CT-flebografie driedimensionele beelden van hoge kwaliteit levert, dit meer invasieve onderzoek geen functionele informatie toevoegt in vergelijking met de echodoppler.

THERAPEUTISCHE PROCEDURES

Compressie en medicatie

Het literatuuronderzoek reikt de volgende bevindingen aan met betrekking tot compressie en medicatie.

- Een systematische review besloot dat een aantal studies van lage kwaliteit wezen op een mogelijke doeltreffendheid van compressie op de pijn en symptomen die gepaard gaan met spataders.
- Een Cochrane-review analyseerde de impact van de zogenaamde "veno-actieve geneesmiddelen" (rutosiden (bijvoorbeeld Venoruton®), calciumdobesilaat (Doxium®, niet beschikbaar in België), planten) bij chronisch veneuze insufficiëntie. Er zijn onvoldoende gegevens om het gebruik van deze medicatie aan te bevelen. Bovendien bleek uit een studie die calciumdobesilaat vergeleek met placebo bij patiënten met chronische veneuze insufficiëntie dat er geen significant verschil tussen de groepen was voor de resultaten die beoogd werden in het studieopzet (levenskwaliteit, oedeem en symptomen na drie maanden behandeling).

Thermische ablatie door endoveneuze laserbehandeling en door radiofrequentie

De studies met betrekking tot thermische ablatie zijn beperkt van omvang en hebben een opvolgingsperiode van maximaal twee jaar. De studies over endoveneuze laserbehandeling tonen geen significant verschil (percentage recidieven) tussen deze techniek en de klassieke chirurgie. Het percentage klinisch recidief (CEAP-classificatie) na één jaar bedraagt ongeveer 10%.

De studies met betrekking tot radiofrequentie-ablatie tonen evenmin dat deze techniek superieur zou zijn op het vlak van klinische doeltreffendheid op korte termijn (maximum 20 maanden), vergeleken met endoveneuze lasertherapie en met klassieke chirurgie.

De resultaten op het vlak van tevredenheid van de patiënten en de evaluatie van hun levenskwaliteit zijn beter bij deze twee nieuwe technieken dan bij klassieke chirurgie. Sommige auteurs vermelden bovendien een sneller hernemen van de gewone activiteiten na een ingreep met behulp van laser of radiofrequentie (2 of 3 dagen) dan na klassieke chirurgie (een tiental dagen).

Chemische ablatie: sclerotherapie met injectie van vloeistof of schuim

De klinische studies met betrekking tot sclerotherapie zijn groter in omvang (> 30 patiënten). De opvolging is van korte duur voor schuimsclerotherapie (maximum 2 jaar), maar kan tot tien jaar gaan voor vloeistofinjecties. Deze studies analyseren de resultaten meestal in termen van het echodoppler beeld, maar geven weinig informatie met betrekking tot de klinische resultaten (symptomen, recidief). De doeltreffendheid van sclerotherapie na enkele maanden (op basis van het percentage occlusie op echodoppler) is vergelijkbaar met die van klassieke chirurgie. Op lange termijn (opvolging van maximum tien jaar) is het percentage recidief van de spataders lager met chirurgie (ongeveer 40%), dan met vloeistofsclerotherapie (ongeveer 50%). De gemiddelde duur van arbeidsongeschiktheid is korter na sclerotherapie (2 dagen) dan na klassieke chirurgie (8 dagen).

Schuimsclerotherapie lijkt effectiever dan vloeistofsclerotherapie, maar de auteurs baseren hun conclusies alleen op de occlusiegraad van de venen tijdens de controle met doppler echografie.

Bijwerkingen van de klassieke chirurgie en van de endoveneuze behandelingen

Pijn, kneuzingen en hematomen komen bij al deze interventies voor. Uit studies blijkt dat deze bijwerkingen en post-operatieve infecties evenwel frequenter zijn na klassieke chirurgie (tussen 2 en 5 %) dan na de andere technieken (meestal < 1%).

Sommige complicaties lijken specifiek na bepaalde procedures vaker voor te komen, zoals pigmentatie na laser (3 % in een prospectieve studie) of na schuimsclerotherapie (1-10 %).

Het opzet van de studies laat doorgaans niet toe om de incidentie van ernstige complicaties nauwkeurig te bepalen. Voor lasertherapie raamt een systematische review de frequentie op minder dan 1% (zenuwletsels, diepe veneuze trombosen en longembolieën). Voor sclerotherapie meldt een Frans register (12.173 sessies) een incidentie van diepe veneuze trombosen van 0,09 % tot 0,2 % na schuimsclerotherapie (versus < 0,1% met vloeistof). Een aantal gevallen van cerebrovasculair accident (CVA) en transient ischaemic attack (TIA) werden beschreven na sclerotherapie, vooral bij gebruik van schuim.

Uiteenlopende anesthesietechnieken al naargelang de studies

Het literatuuronderzoek identificeerde geen enkel klinisch onderzoek dat zich specifiek richtte op de anesthesietechnieken voor interventies bij spataders in de benen. Er bestaan dus geen gegevens die een of andere anesthesietechniek kunnen koppelen aan klinische resultaten.

Lokale tumescentie-anesthesie is een techniek die steeds meer wordt gebruikt in het kader van endoveneuze procedures. Bij deze techniek wordt een grote hoeveelheid verdund lokaal anestheticum ingespoten om opzwelling van de weefsels te bekomen. Deze techniek heeft niet alleen een anesthetisch effect, maar beschermt ook de weefsels rond de ader en vergemakkelijkt de ingreep.

De analyse van de technieken gebruikt in therapeutische klinische onderzoeken kan als volgt worden samengevat:

- Algemene anesthesie en spinale anesthesie zijn de technieken die het meest gebruikt worden in de studies met betrekking tot spataders van de benen (klassieke chirurgie, laserablatie of radiofrequentie);
- Thermische ablatietechnieken (laser, radiofrequentie) worden ook uitgevoerd onder lokale tumescentie-anesthesie .
- Sclerotherapie heeft het voordeel dat het kan worden uitgevoerd zonder anesthesie.

BESPREKING EN BESLUIT

Wat betreft de diagnose, is er één studie die aantoont dat kleuren-echodoppler wel degelijk het pre-operatief refentieonderzoek is, want het vermindert het risico op recidief en heringreep. Er werd geen enkele studie aangetroffen die pleit voor andere onderzoeken om de echodoppler te vervangen of aan te vullen.

Compressie (kousen, verbanden) zou enige doeltreffendheid hebben voor het verbeteren van de symptomen die gepaard gaan met spataders in de onderste ledematen, maar de bewijzen zijn van lage kwaliteit. De therapietrouw ligt evenwel meestal laag, maar de studies houden hier doorgaans geen rekening mee.

De beschikbare gegevens tonen geen doeltreffendheid van de zogenaamd 'veno-actieve' geneesmiddelen (rutosiden, calciumdobesilaat, planten).

Enkele maanden na de ingreep blijkt de doeltreffendheid van endoveneuze technieken vergelijkbaar met die van de klassieke chirurgie, maar met minder post-operatieve complicaties. De validiteit van deze vaststelling wordt echter beperkt door de zwakke kwaliteit van de momenteel beschikbare studies:

- ze zijn beperkt qua omvang (meestal slechts enkele tientallen patiënten),
- voor eenzelfde operatietechniek verschilt de apparatuur tussen de studies en evolueert ze ook in de loop van de tijd (de huidige technieken zijn van een jongere generatie dan die beschreven in de literatuur),
- de evaluatie van de doeltreffendheid is steeds gebaseerd op echografische metingen (zonder gewag te maken van de klinische repercussies), minder vaak op klinische metingen ("hard outcomes": symptomen, recidief),
- de meetschalen variëren (pijn, levenskwaliteit),
- de opvolgingsperiode beloopt zelden meer dan enkele maanden.

De heterogeniteit van de studies liet niet toe om een globale meta-analyse uit te voeren. Bovendien gaan deze bevindingen voornamelijk over patiënten met spataders in een vroeg klinisch stadium (C2 en C3): er kon geen enkele conclusie worden getrokken wat betreft de beste behandelingskeuze in functie van het klinisch stadium van de spataders. Er is ook geen evidentie ter ondersteuning van het gelijktijdig gebruik van twee verschillende invasieve technieken op hetzelfde been: slechts enkele studies keken naar de combinatie van sclerotherapie met klassieke chirurgie.

Er werd ook geen enkele studie gevonden die toeliet om te bepalen welke anesthesietechniek het best geschikt is voor welke interventie. Thermische ablatietechnieken (laser, radiofrequentie) bieden echter het voordeel dat ze kunnen worden uitgevoerd onder lokale tumescentie-anesthesie, terwijl sclerotherapie zelfs geen anesthesie vereist.

Momenteel zijn de thermische ablatietechnieken niet voorzien in de nomenclatuur en de meeste ingrepen voor spataders gebeuren momenteel via daghospitalisatie, onder locoregionale of algemene anesthesie. In andere Europese landen (bijvoorbeeld Nederland) worden de ingrepen grotendeels uitgevoerd in een strikt ambulant kader, onder lokale tumescentie-anesthesie, vaak opgesplitst in meerdere sessies.

AANBEVELINGEN[a]

- **Echodoppler is de diagnostische techniek die momenteel wordt aanbevolen om therapeutische beslissingen met betrekking tot spataders van de onderste ledematen te oriënteren.**
- **Thermische ablatietechnieken (laser, radiofrequentie) en sclerotherapie kunnen aanbevolen worden als alternatieven voor de klassieke chirurgie: de resultaten zijn vergelijkbaar op middellange termijn en de technieken kunnen worden uitgevoerd onder lokale anesthesie, of zelfs zonder anesthesie voor sclerotherapie.**
- **Er is een aanpassing van de nomenclatuur nodig die deze nieuwe technieken een plaats geeft en hun gebruik in ambulante omgeving onder lokale anesthesie (of zelfs zonder anesthesie voor sclerotherapie) bevordert voor de behandeling van spataders zonder complicaties.**
- **Registratie van ernstige complicaties en recidieven is nodig om de veiligheid en de doeltreffendheid op lange termijn van deze nieuwe technieken na te gaan (vooral voor wat betreft het gebruik van schuimsclerotherapie).**
- **De huidige gegevens laten niet toe om aanbevelingen te doen met betrekking tot het nut van compressie bij de behandeling van spataders van de onderste ledematen.**
- **Medicamenteuze behandelingen worden niet aanbevolen.**

a Het KCE blijft als enige verantwoordelijk voor de aanbevelingen die aan de overheid worden geformuleerd.

Scientific summary

Table of contents

ABBREVIATIONS

ASERNIP	Australian Safety and Efficacy Register of New Interventional Procedures
AVVQ	Aberdeen Varicose Veins Questionnaire
BLARA	Bilateral varicose veins
CEAP	Clinical class, Etiology, Anatomy, Pathophysiology
CHIVA	Conservative Hemodynamic Management of Varicose Veins
CIVIQ	Chronic Venous Insufficiency Questionnaire
CT	Computed tomography
CVD	Chronic Venous Disease
DET	Data extraction table
DUS	Colour duplex ultrasonography/duplex scan
DVT	Deep vein thrombosis
EVLT/ EVLA	Endovenous laser therapy / ablation
EQ-5D	EuroQol – 5D (questionnaire)
HAS	Haute Autorité de Santé
HHD or CADU	Hand held Doppler or continuous-wave Doppler ultrasound
INAHTA	International Network of Agencies for Health Technology Assessment
GA	General anaesthesia
GSV	Great saphenous vein
LA	Local anaesthesia
LSV	long saphenous vein
MDCT	Multidetector computed tomography
MHCS	Modified Hollander Cosmetic Score
MRI	Magnetic resonance imaging
NHS	National Health Service (UK)
NIHDI	National Institute for Health and Disability Insurance
NPV	Negative predictive value
PPV	Positive predictive value
QoL	Quality of life
RCT	Randomised controlled trial
RFA	Radiofrequency Ablation
SF-36	Short-form 36 (questionnaire)
SFJ	Saphenofemoral junction
SFL/S	Sapheno-femoral ligation and stripping
SIGN	Scottish Intercollegiate Guidelines Network
SPJ	Saphenopopliteal junction
SR	Systematic review
SSV	Small or Short saphenous vein
TLA	Tumescent Local Anaesthesia
VAS	Visual analogue scale
VCSS	Venous Clinical Severity Scores

1 INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Diagnostic and therapeutic procedures for varicose veins rapidly evolved during the last decade. However billing codes used in Belgium are still based on the use of conventional techniques whilst new endovenous procedures are increasingly used[1].

1.1.1 Necessary update of billing codes

Data from the National Institute for Health and Disability Insurance (NIHDI) show disparities in the use of billing codes for anaesthetic as well as in diagnostic and therapeutic procedures[2]. For example, the annual number of interventions reimbursed based on the billing codes 589411-589422 [2] ("percutaneous occlusion of arterial or venous vessels using medical imaging") increased from 1 023 in 2005 to 8 772 in 2008. The use of this code later decreased following changes in the definition of this medical act. Currently there is no specific code for endovenous procedures. Haxhe et al. carried out a survey among members of the Belgian Society of vascular surgery[1]. They found a significant difference between the figures reported by the surgeons (33% endovascular techniques) versus official data from the NIHDI (18%). The authors interpreted this discrepancy by a sampling bias (52 out of 238 members) but also by the inappropriateness of the current billing codes to report the new endovenous techniques.

The NIHDI statistics[2] also triggered a complementary question in relation to the type of anaesthesia used in the interventions for varicose veins. Nearly half of the billing codes for these interventions (42%) are coupled with a billing code for general anaesthesia, 15% have a billing code for locoregional anaesthesia and one third of the interventions combine codes for general and locoregional anaesthesia (36%). Billing codes for operating aid are reported in about 50% of the interventions.

1.1.2 Use of obsolete diagnostic techniques

For diagnostic procedures a guideline has been elaborated by the Consilium Radiologicum and published on the website of the Federal Public service Health, Food security and Environment[3]. This guideline recommends the use of colour duplex Doppler ultrasound in most cases. Magnetic resonance imaging (MRI), tomography (and phlebography) might be used in exceptional cases (e.g. congenital abnormalities) before an intervention. The NIHDI subsequently sent a document to all physicians on the rational use of imaging procedures to decrease the risk linked to ionizing radiation4. Data illustrated e.g. the use of phlebography in 2008. They estimated the desirable reduction in use of phlebography in Belgium to be around 76%.

The emergence of the new endovenous techniques, coupled with the uncertainty about the use of outdated billing codes, triggered the submission of a topic proposal to the KCE by the NIHDI.

The objective of this research is to identify the best available evidence on the diagnosis and treatment of varicose veins of the lower limbs.

1.2 CLINICAL BACKGROUND: VARICOSE VEINS

1.2.1 Definition

The condition of varicose veins has been defined as permanently dilated subcutaneous veins equal to or more than 3 mm in diameter in the upright position [5]. Patients with varicose veins of the lower limbs typically present with abnormal sensation (itching, aching, tingling), leg pain, fatigue and heaviness, swelling and restless leg syndrome with prolonged standing [6, 7]. These symptoms are associated with clinical signs, such as dilated tortuous veins (veins are twisted, swollen, and visible under the skin) and oedema.

Complications are leg ulcers, thrombophlebitis and other pathological skin changes (e.g. dermatitis) [7, 8].

1.2.2 Prevalence

Estimates for prevalence vary based upon population, selection criteria, disease definition and imaging techniques. Prevalence increases with age and the following figures have been reported by different studies[9]:

- In a population-based study (Bonn Vein Study[10]) classification levels were 59.0% for C1, 14.3% for C2, 13.5% for C3, 2.9% for C4 and 0.7% for C5-C6;
- Estimates in the adult population from UK ranged from 20% to 40%[11].
- Occurrence in Europe and the USA is estimated to be 25% to 30% in adult women and approximately 15% in adult men[11].
- The age stratified prevalence of trunk varices measured in the Edinburgh Vein study was 11.5% in the 18-24 age group increasing to 55.7% in the 55-64 age range[12 13].

1.2.3 Aetiology and risk factors

The aetiology of varicose veins remains elusive[14] but is likely to be multifactorial. Varicose veins might result from abnormal elastic properties of the venous wall[7]. Valve damage is the most common aetiology of primary varicose veins, leading to increased pressure and distension of the veins[15].

Risk factors include high intravenous pressure (due to standing for long periods), sedentary lifestyle, pregnancy, gender, and family history, although genetic factors have not been proven[16, 17]. Obesity itself is not a risk factor; however obese people with varicose veins have a higher complication rate[17]. Smoking in men has been shown to be also a risk factor[18]. Previous deep vein thrombosis is the most frequent cause of secondary varicose veins [7, 14].

1.2.4 Disease severity: CEAP Classification

Disease severity is commonly classified using the CEAP classification (Table 1): Clinical, Etiologic, Anatomic and Pathophysiologic classifications[19 20].

Table 1: CEAP classification (adapted from Kundu et al. 2010[19])

Clinical Classification	**Description**
C0	No visible or palpable signs of venous disease
C1	Telangiectases or reticular veins
C2	Varicose veins: distinguished from reticular veins by a diameter of 3mm or more
C3	Oedema
C4	Changes in skin and subcutaneous tissue secondary to venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer
Etiologic classification	

Ec	Congenital
Ep	Primary
Es	Secondary
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Obstruction
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

The question to know the stage when varicose veins need to be treated remains unsolved. The Bonn Vein study mentioned in 1.2.2 currently analyses the progression of the disease over a long-term period. The decision to operate might also be based on aesthetic grounds or on the reimbursement rules that vary between countries or insurance schemes (cf. USA)[21].

1.3 RESEARCH QUESTIONS

This systematic review addresses the following research questions for the diagnosis and treatment of varicose veins of the lower limbs:

1. What is the value of diagnostic procedures to confirm the clinical diagnosis of varicose veins, assess the severity and decide upon treatment?
2. What are the clinical effectiveness and safety of available treatments (conservative and surgical treatments)?
3. Is there available evidence on the type of anaesthetic most appropriate for each intervention?

1.3.1 First research question: diagnostic procedures

1.3.1.1 Patient population

Publications had to include adult patients with a clinical diagnosis of varicose veins of the lower limbs.

Exclusion criteria were: varicose veins at other locations, studies on patient populations with chronic venous insufficiency in general, no report of results by CEAP classification subgroups, other pathology of the veins (e.g. thrombophlebitis), pregnant women, treatment of complications.

1.3.1.2 Diagnostic tests

The diagnostic tests considered for inclusion in collaboration with the consulted Belgian experts are listed in section 1.4.

1.3.1.3 Outcomes

- Diagnostic accuracy outcomes used to measure venous reflux and determine the position of reflux e.g. sensitivity, specificity, likelihood ratios;
- Clinical consequences of diagnostic test i.e. how the test affects the treatment plan or influences unnecessary treatment. However papers were excluded if they only reported surgical efficacy outcomes without reference to the diagnosis.

Papers were excluded if they only described other outcomes e.g. related to costs, to anatomical measures of reflux.

1.3.2 Second research question: effectiveness and safety of treatments

1.3.2.1 Patient population

Publications had to include adult patients with a confirmed diagnosis of varicose veins of the lower limbs. Exclusion criteria were the criteria described in 1.3.1.1 and venous abnormalities.

1.3.2.2 Interventions

The interventions and comparators considered for inclusion are listed in Table 2. Interventions that specifically targeted venous ulcers were excluded (e.g. dressings, dressings, laser therapy).

1.3.2.3 Comparators

The comparators considered for inclusion are usual care, no intervention or the treatments listed in Table 2.

1.3.2.4 Outcomes

The effect on "hard" outcomes were included i.e. clinically relevant symptoms, complications, quality of life, reoperations and adverse events. The occlusion and recurrence rates are mentioned as intermediate outcomes.

1.3.3 Third research question: type of anaesthetic for each intervention

The patient population and outcomes are similar to those described under 1.3.2.

The types of interventions considered were general, spinal, regional and tumescent local anaesthesia.

Tumescent local anaesthesia is a procedure commonly used in varicose vein treatment with two objectives. The first one is pain control of the treated area. The second one is the injection of liquid around the vein to protect the surrounding tissue and to facilitate the intervention. Tumescent solution can vary according to the clinician's preference but usually consists of a saline solution with added lidocaine, epinephrine and sodium bicarbonate. Using ultrasound guidance, this solution is infused under pressure in the saphenous compartment around the vein: at the conclusion of anaesthesia infiltration the vein is maximally compressed and appears on duplex ultrasound to be floating in a 'sea' of anaesthetic solution[22].

1.4 DIAGNOSIS OF VARICOSE VEINS

The diagnosis and treatment of varicose veins are generally guided by an assessment of patient's risk factors and symptoms as part of a clinical examination. However, according to expert clinicians, clinical tests such as the cough test, the tap test, Trendelenbergs' test and Perthes' test, are not used anymore in modern practice. Several studies[23] [24] have validated the inaccuracy of these tests and they will not be discussed further.

The paragraph below briefly outlines the choice of the diagnostic tests selected for this report, based on the feedback of the expert clinicians consulted for this study.

- Colour Duplex ultrasound is used as the 'gold standard' reference test for the diagnosis of varicose veins and to assess the severity of the disease[3] [25], also to locate the insufficient perforators or the junction of the small saphenous vein (SSV). In Belgium this procedure is increasingly performed by the surgeon him/herself, also preoperatively[1]. Performing colour duplex ultrasound (with the patient standing) in each leg of an individual patient with varicose veins leads to a full understanding of haemodynamics and anatomy, namely the so called 'duplex anatomy' (which specifically addresses the role of refluxing saphenous trunks, great saphenous vein (GSV), anterior accessory saphenous vein, SSV, on one hand and the role of the tributaries on the other hand). This will determine which treatment should be performed in each patient[26].

- Preoperative Arterial Doppler might be coupled with the previous one to ensure that the blood supply is adequate for healing the area;
- Specific techniques like phlebography, magnetic resonance imaging and computed tomography (CT venography) are used for certain conditions, such as evaluation of venous anomalies[19 27];
- In the USA intravascular ultrasound is also used, mainly to diagnose venous abnormalities[28].

Hand-held Doppler (HHD) or continuous-wave Doppler ultrasound is described in the literature: it has been used in outpatient clinics despite its low accuracy because it was quick, inexpensive and non-invasive but it is not use anymore in current practice.

Other imaging techniques previously used include venography, volumetry and plethysmography[16]. They were not within the scope of this study.

1.5 TREATMENT OPTIONS FOR VARICOSE VEINS

Treatment options are generally divided into conservative approaches and surgical interventions (Table 2). Among the surgical techniques, endovenous ablation techniques (radiofrequency, laser, steam and sclerotherapy) are modern alternatives to the traditional ligation and stripping of the saphenous veins.

Table 2: Interventions for varicose veins

Conservative

- Lifestyle modifications e.g. weight loss, avoidance of long standing
- Exercise
- Elevation of affected legs
- Support stockings/compression stockings/intermittent pneumatic compression devices
- Drugs

Surgical therapy

- Traditional surgery (e.g. stripping, ligation, phlebectomy)
- Thermal ablation of a refluxing trunk
  - radiofrequency ablation (RFA)/
  - laser (EVLT)
  - steam
- Sclerotherapy of a refluxing trunk and/or tributaries
  - liquid sclerotherapy
  - foam sclerotherapy
- Phlebectomies only
- Mixed treatments

1.5.1 Traditional surgical procedures

Surgery is the traditional treatment that usually involves saphenous junction ligation and stripping of the great saphenous vein (GSV) from the groin to the knee, or the small saphenous vein (SSV) from the knee to the mid calf [29].

Ligation involves tying off the great or small saphenous veins at the saphenofemoral junctions (SFJ) or saphenopopliteal (SPJ) respectively, with additional ligation of the side-branches as the inferior epigastric vein or pudendal vein.

Stripping involves insertion of a stripper into the saphenous vein; the vein is then attached to the end of the stripper, which is gently withdrawn, and the vein is removed through the point of exit[30]. This technique may be supplemented by multiple phlebectomies for the tributaries, which involve the use of a vein hook to allow removal of superficial varicosities through small stab incisions[31] or insufficient perforator ligature through small stab incisions after locating them with Duplex ultrasound (DUS).

Other surgical techniques developed for the removal of superficial varicosities or insufficient perforators (i.e. transilluminated powered phlebectomy and subfascial endoscopic perforator vein surgery) are not within the scope of this report[29 32].

1.5.2 Endovenous Laser Therapy

Endovenous laser therapy (EVLT) is a minimally invasive treatment of varicose veins. The procedure involves introduction of a laser fibre into the lumen of the saphenous vein, followed by the application of laser energy which destroys the vein wall after local injection of fluid to cause tumescence around the treated vein. The fibre and catheter are slowly withdrawn and the vein lumen collapses, occluding the length of the vein and abolishing venous reflux[33].

1.5.3 Radiofrequency Ablation

A similar technique to EVLT is radiofrequency ablation (RFA).

A heat-generating catheter inserted into the vein emits radio-frequency wavelengths for ablation[33]. After tumescent injection, the catheter is heated and slowly withdrawn down the length of the vein, causing contraction of the vein wall and, ultimately, destruction of the vessel [29, 34].

1.5.4 Sclerotherapy

Sclerotherapy involves injecting a sclerosing agent (polidocanol) into the varicose vein, which triggers an inflammatory reaction in the endothelium, causing phlebitis and vein occlusion[35].

Foam sclerotherapy mixes the liquid sclerosant with gas to create a larger surface area by displacing blood within the vein[36]. Foam sclerotherapy can be used for treating the GSV or the SSV or to treat the tributaries. The dose is adapted to the diameter of the treated vein.

1.5.5 Mixed treatments

In practice, many surgeons perform a mix of treatments such as surgical ligation and stripping combined with sclerotherapy or EVLT combined with sclerotherapy.

2 METHODS

2.1 SEARCH STRATEGIES

2.1.1 Diagnostic techniques for varicose veins

The following databases were systematically searched for the diagnostic procedures:

- The Cochrane Library
- OVID Medline
- OVID EMBASE
- Medion

The search strategies (available upon request) combined descriptors of varicose veins and terms describing each of the diagnostic procedures mentioned in 1.4.

The search focused on the last 15 years upon advice of the experts clinicians: the rapid evolution of the techniques in this area made the results of older trials obsolete for current practice. One illustration is the use of hand-held doppler, currently replaced by colour duplex ultrasound.

2.1.2 Treatment of varicose veins

The wealth of literature on the treatment of varicose veins made a de novo systematic review of literature impractical. In order to manage the volume of literature anticipated, the search was segmented into two phases. During the first phase, systematic reviews of treatments were included. The last systematic review of high quality was identified and the list of its constituent primary studies (RCTs and controlled trials) was completed by the trials included in other systematic reviews. In a second phase the most recent RCTs and controlled trials published after the search date of this systematic review were added.

2.1.2.1 Search for systematic reviews

The following databases were systematically searched in October 2010 for systematic reviews:

- The Cochrane Library
- OVID Medline
- OVID EMBASE

Databases were searched for publications in English, French, Dutch or German (search strategies available upon request). The initial date limit was 1990 to capture all possible relevant literature. However, given the rapid evolution of treatments and the high number of available systematic reviews (rated as having a low risk of bias), only reviews since 1999 have been considered.

Additional hand searching was also undertaken to ensure that no potentially relevant studies were missed. The reference lists of retrieved articles and existing systematic reviews were scanned and websites of INAHTA members were checked in detail (see Appendix 9.1).

2.1.2.2 Search for RCTs

The same databases (and www.clinicaltrials.gov) were systematically searched for RCTs of treatment of varicose veins. The treatment searches were limited from 2008 as this was the search date in the most recent selected systematic review (from Rees et al.[29]). An additional literature search for the drug treatment of varicose veins was limited from 2005 as this was the date of the search from the most recent systematic review in this area[37].

Additional hand searching of reference lists was also undertaken to ensure that no potentially relevant studies were missed.

2.2 ASSESSING METHODOLOGICAL QUALITY AND RISK OF BIAS

2.2.1 Diagnostic studies

The methodological quality of diagnostic studies was assessed using the QUADAS tool[38] by a team of three reviewers (FA, MK, SM). The papers were divided amongst the three reviewers and then swapped over for double quality assessment. Any uncertainties were discussed between the three reviewers. The QUADAS tool is structured as a list of 14 questions addressing aspects of the study design such as patient population, the reference and index tests and whether there is blinding of the tests (see appendix 9.2.1). These questions are scored "yes", "no" or "unclear" and an assessment of the methodological quality of each study involved investigation of the individual quality items rather than using a combined quality score[38]. The results are in appendix 9.2.2.

2.2.2 Systematic reviews

The methodological quality of systematic reviews and associated risk of bias were rated using the SIGN tool[a]. This tool uses a scale of ratings ranging from (well covered, adequately addressed, not addressed, not reported and not applicable).The assessment of the risk of bias in the included SRs was conducted by a team of three reviewers (FA,MK,SM) who pre-agreed the ratings before beginning quality analysis. In order for systematic reviews to be included, three of the four following criteria had to be rated as "well covered" or "adequately addressed":

- Appropriate and clearly focussed study question;
- Description of methodology; sufficiently rigorous literature searches (defined according to SIGN SR quality appraisal tool e.g. Medline, EMBASE, Cochrane and hand searching of reference lists);
- Quality and methodological strengths and weaknesses of identified data assessed and taken into account.

The results of the quality appraisal of systematic reviews are in Appendix 9.3.

2.2.3 Randomised controlled trials

The methodological quality of selected RCTs was rated using a modified version of the SIGN tool. The assessment of the risk of bias in the included RCTs was conducted by a team of three reviewers (FA, MK, SM). In order for RCTs to be included, two of the four following criteria had to be rated as "well covered" or "adequately addressed":

- Randomisation;
- Blinding of outcome assessment;
- Treatment groups comparable at baseline;
- Description of dropouts and withdrawals.

The quality appraisal tool and the results are in Appendix 9.5.

2.3 DATA EXTRACTION

2.3.1 Diagnostic studies

The DET for diagnostic studies captured the following information: reference, country, patient numbers and characteristics, index test, reference test, diagnostic accuracy outcomes e.g. sensitivity, specificity, clinical significant outcomes e.g. decision to perform surgery, results and description of quality appraisal (see appendix 9.2.3).

Data extraction of the papers was performed by a reviewer (FA) into a pre-prepared Word® table. Extraction was verified in full by a second reviewer (MK). Any discrepancies were resolved through discussion with the third reviewer (SM).

[a] http://www.sign.ac/methodology/checklists.html

2.3.2 Systematic reviews

Data from systematic reviews and from trials were extracted into a specifically designed data extraction table (DET) in order to summarise key design features and results. Results of quality assessment were also recorded. The DET of the systematic reviews captured the following information: reference, details of searches, inclusion and exclusion criteria, specific intervention, number and types of studies included, outcomes, efficacy and safety results, information regarding anaesthesia used and a summary of study conclusions (see appendix 9.4).

2.3.3 Randomised controlled trials

The DET for RCTs captured the following information: reference, country, patient numbers and characteristics, details of intervention, details of comparator, outcome, time of follow-up, efficacy results, details of complications/adverse events, quality of life data and interpretation of results (see appendix 9.6).

The assessment of risk of bias and the data extraction were performed by a reviewer (FA) into a pre-prepared Excel® spreadsheet. Extraction was verified in full by a second reviewer (MK). Any discrepancies were resolved through discussion with an independent third party (SC).

A level of evidence has been attributed after the analysis of the available evidence based on the GRADE classification[39].

3 RESULTS: DIAGNOSTIC PROCEDURES FOR VARICOSE VEINS

3.1 IDENTIFIED STUDIES AND QUALITY APPRAISAL

3.1.1 Selection of two diagnostic studies

The literature search for relevant diagnostic RCTs was carried out in January 2011 identifying 933 citations. The majority of citations were excluded on the basis of title and abstract, mainly because the population or interventions were without the scope of this study. The other papers (n=18) were retrieved in full and reviewed in detail. Due to the low number of relevant trials an additional database search of Medline and EMBASE was carried out in May 2011 with a search strategy designed to capture observational studies. This search yielded 921 citations but no new relevant studies were identified from this search. The reference lists of all relevant articles and reviews were scanned to identify any further relevant studies.

On the basis of the full text, seven of the 18 studies were excluded :

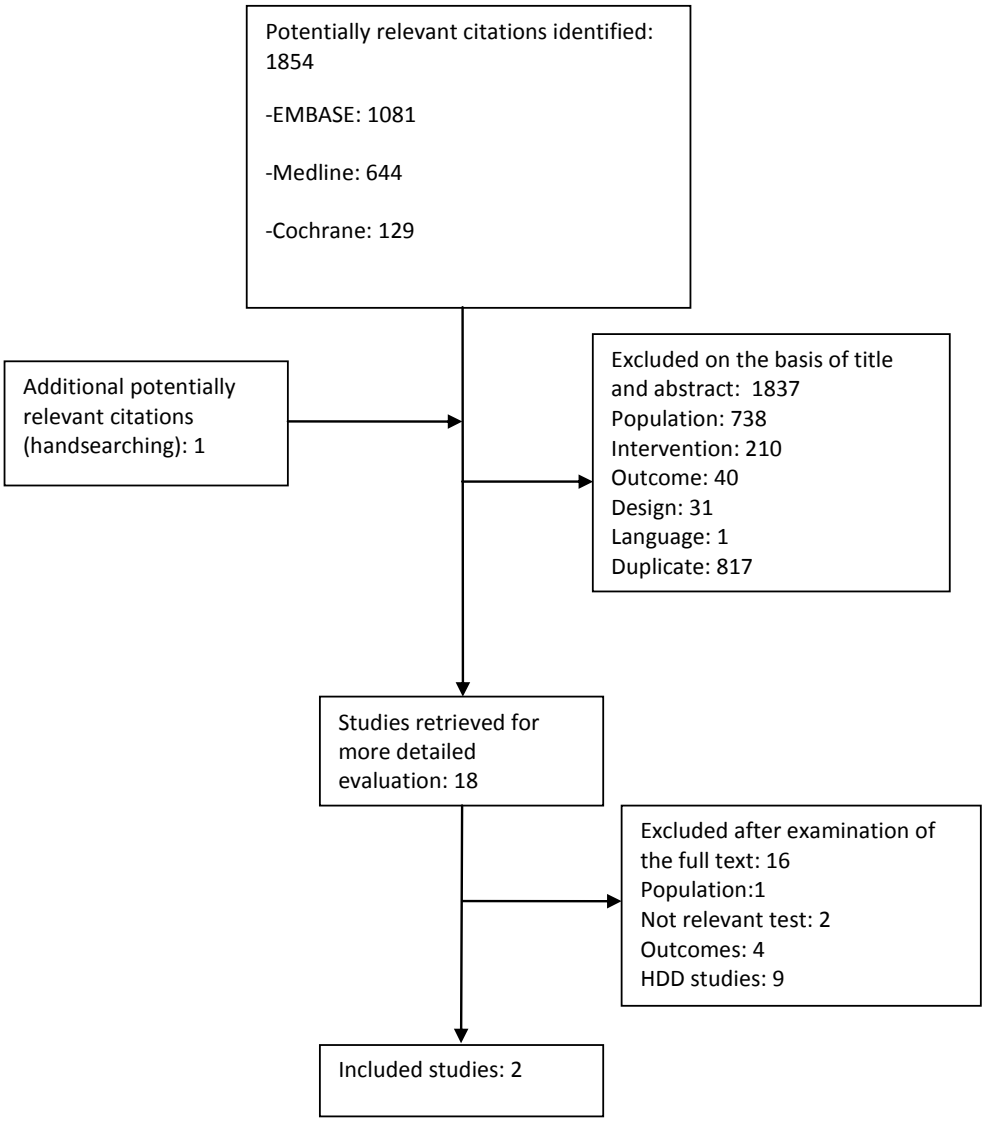
- two evaluated clinical examination as the index test40 41;
- four had outcomes not relevant to diagnosis such as cost data or prevalence of reflux at different anatomical sites42-45;
- one studied incompetent perforating veins, a patient group out of the scope of this review46.

Nine other studies on hand-held doppler were further excluded upon the advice of experts and validators. This technique has not been in use in many years: in 2006 an international consensus agreed upon the role of duplex ultrasound for the pre-operative assessment of varicose veins[26]. The quality and results of these nine studies can be found in appendix 9.2.4 and 9.2.5.

Therefore, two studies were finally included and assessed for their methodological quality.

Figure 1 shows the results of the literature searches and flow of studies.

Figure 1 Results of searches and selection of diagnostic studies



3.1.2 Quality appraisal of diagnostic studies

Quality appraisal was carried out using the QUADAS tool[38] as discussed in section 2.2.1. Figure 2 shows the range of quality rating per question of the QUADAS tool. The two studies were judged to have a low risk of bias as they studied patients representative of usual practice, used an acceptable reference test (duplex ultrasound) and patients underwent this test regardless of the results of the index test.

Figure 2 Quality appraisal results using QUADAS [38]tool

	Blomgren	Lee
pts representative of normal practice?	✓	✓
selection criteria defined?	✓	✓
acceptable ref standard?	✓	✓
acceptable delay between tests?	NA	✓
partial verification avoided?	✓	✗
differential verification avoided?	✓	✓
ref standard independent of index test?	✓	✓
index test described in detail?	✓	✓
ref standard described in detail?	✓	✓
index tests blinded?	!	✗
ref test blinded?	!	✗
relevant clinical information?	✓	✓
uninterpretable results reported?	✓	✓
withdrawals explained?	✓	✓

Key	
✓	yes
!	unclear
✗	no

NA: not applicable

3.2 OVERVIEW OF INCLUDED DIAGNOSTIC STUDIES

The two studies included compared a reference test, duplex ultrasound scan before varicose vein surgery, with:

- no duplex ultrasound[47],
- duplex ultrasound with CT venography[48].

No studies were found for the diagnostic procedures of preoperative arterial Doppler, phlebography, magnetic resonance imaging and intravascular ultrasound.

3.3 PRE-OPERATIVE DUPLEX ULTRASOUND COMPARED WITH NO SCAN

Blomgren (2005) compared duplex with no duplex (clinical examination) and as such evaluated the clinical outcomes associated with a patient undergoing a duplex scan prior to varicose vein surgery. Patients (343 legs) were randomised to either duplex imaging or no duplex before varicose vein surgery and followed up at two months and two years with a duplex assessment. Duplex imaging conducted before surgery resulted in a different clinical plan compared with clinical examination in 26.5% of legs. At two years, two legs had recurrence compared with 14 legs in the in the non-duplex scan group ($p=0.002$)[47].

3.4 COMPUTED TOMOGRAPHY VERSUS DUPLEX

A study by Lee et al. (2008) used multidetector computed tomography (MDCT) to evaluate 100 patients (151 limbs) with varicose veins. They performed a comparative analysis with duplex in 50 patients only (61 limbs)[48]. The authors concluded that CT images provide a good 3D overview of the deep venous system. The sensitivity of CT venography in the prediction of GSV insufficiency was 98.2% (56 of 57 cases) and the specificity was 83.3% (14 of 17 cases). MDCT was less accurate in the prediction of insufficiency in the SSV with a sensitivity of 53.3% (eight of 15 cases) and a specificity of 94.9% (56 of 59 cases)[48].

However, this test did not demonstrate any functional information of reflux or valve insufficiency. Given this lack of functional information as well as the disadvantage of the invasive procedure with the use of ionizing radiation there is no evidence that this technique is superior to duplex ultrasound to improve the outcomes of patients with varicose veins.

- **Duplex ultrasound is considered to be the 'gold standard' for the assessment of venous haemodynamics and anatomy (duplex anatomy) to determine the appropriate treatment for each patient;**
- **There is no evidence to recommend multidetector computed tomography or other diagnostic tests for the diagnosis and treatment planning of varicose veins.**

4 RESULTS: INTERVENTIONS FOR THE TREATMENT OF VARICOSE VEINS

4.1 IDENTIFIED STUDIES AND QUALITY APPRAISAL

4.1.1 Systematic reviews

4.1.1.1 Identified studies

A total of 720 citations on the topic of interventions for varicose veins were identified in database searches (Figure 3). The supplementary searches of INAHTA member websites and hand searching yielded 20 additional references. The majority of citations were excluded on the basis of title and abstract; 71 citations were retrieved in full and reviewed in more detail. On the basis of the full text, 32 reviews were included.

4.1.1.2 Results of quality appraisal: 22 systematic reviews selected

As a first step, quality appraisal of the 32 reviews was carried out to determine their suitability for inclusion. Four criteria were used to appraise study quality, using the SIGN tool (see 2.2.2). Ten studies were excluded and 22 systematic reviews were included as detailed below.

Excluded studies

Eight [6 7 49-54] reviews were judged to have been undertaken using less rigorous methods and were labelled as "high risk of bias":

- Five studies [7 49-52] on multiple treatments;
- Coleridge Smith et al.[53] on sclerotherapy;
- Two reviews on EVLT[6 54].

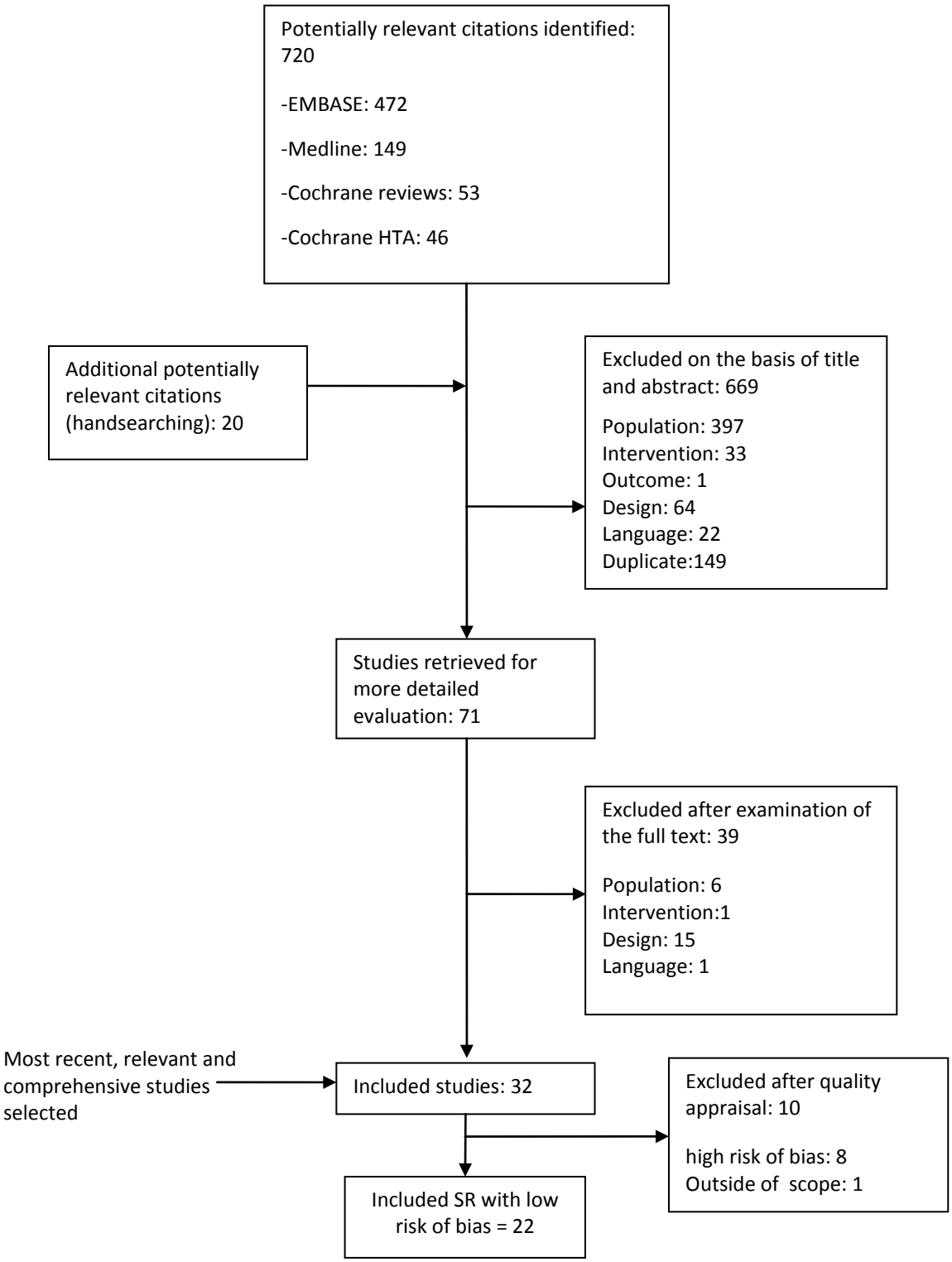
One systematic review with low risk of bias[55] was additionally excluded because it reported little useful information. Another review[32] was also excluded because it evaluated transilluminated powered phlebectomy on varicosities which is out of scope of this review.

Final selection: 22 systematic reviews

Figure 3 shows that 22 of the reviewed studies were judged to be with a low risk of bias (see appendix 9.3): they were further included in the results[29 30 33-37 56-70].Three of these included systematic reviews failed to address the quality of included studies but performed better against other methodological markers[56 60 61].

The methodology of meta-analysis was applied in three other systematic reviews, two by Luebke et al and one by Van Den Bos[32 59 68]. The validity of their conclusions is limited by the heterogeneity of study types, interventions and study population.

Figure 3: Results of searches and selection of systematic reviews



4.1.2 Randomised controlled trials

4.1.2.1 Identified studies

The literature search for relevant RCTs was carried out in February 2011 identifying 1913 citations (figure 4). An additional recently published RCT[71] was identified by one of the experts. The majority of citations were excluded on the basis of title and abstract; the other papers (n=42) were retrieved in full and reviewed in more detail.

In addition, three potentially relevant trials (NCT00621062, NCT00529672, and NCT01103258) were identified in the ClinGov website (www.clinicaltrials.gov). The investigators were contacted to find out when the results of these ongoing trials would be published.

Three RCTs were excluded from the analysis because they had already been discussed in the previous phase on systematic reviews. On the basis of the full text, nine other studies were excluded: eight were not RCTs and one lacked a comparator group. Therefore, 30 RCTs were assessed for their methodological quality.

4.1.2.2 Results of quality appraisal for RCTs

The majority of RCTs (n=24) were judged to have a low risk of bias and six RCTs high risk of bias (see appendix 9.5).

Exclusion of 6 RCTs with high risk of bias

Six RCTs[72-77] had a high risk of bias because authors did not report on the method of randomisation, the baseline characteristics of patient groups, or patient drop outs during the study:

- Two RCTs on sclerotherapy: Hamel-Desnos (2010)[74],Yamaki (2009)[77];
- Two RCTs on EVLT: Maurins (2009)[75],Theivacumar (2008)[76];
- One RCT with EVLT versus RFA: Gale (2010)[73];
- One RCT on surgery (comparison of 2 stripping techniques): Assadian (2008)[72].

24 RCTs with low risk of bias

Twenty-four RCTs had a low risk of bias[71 78-100].

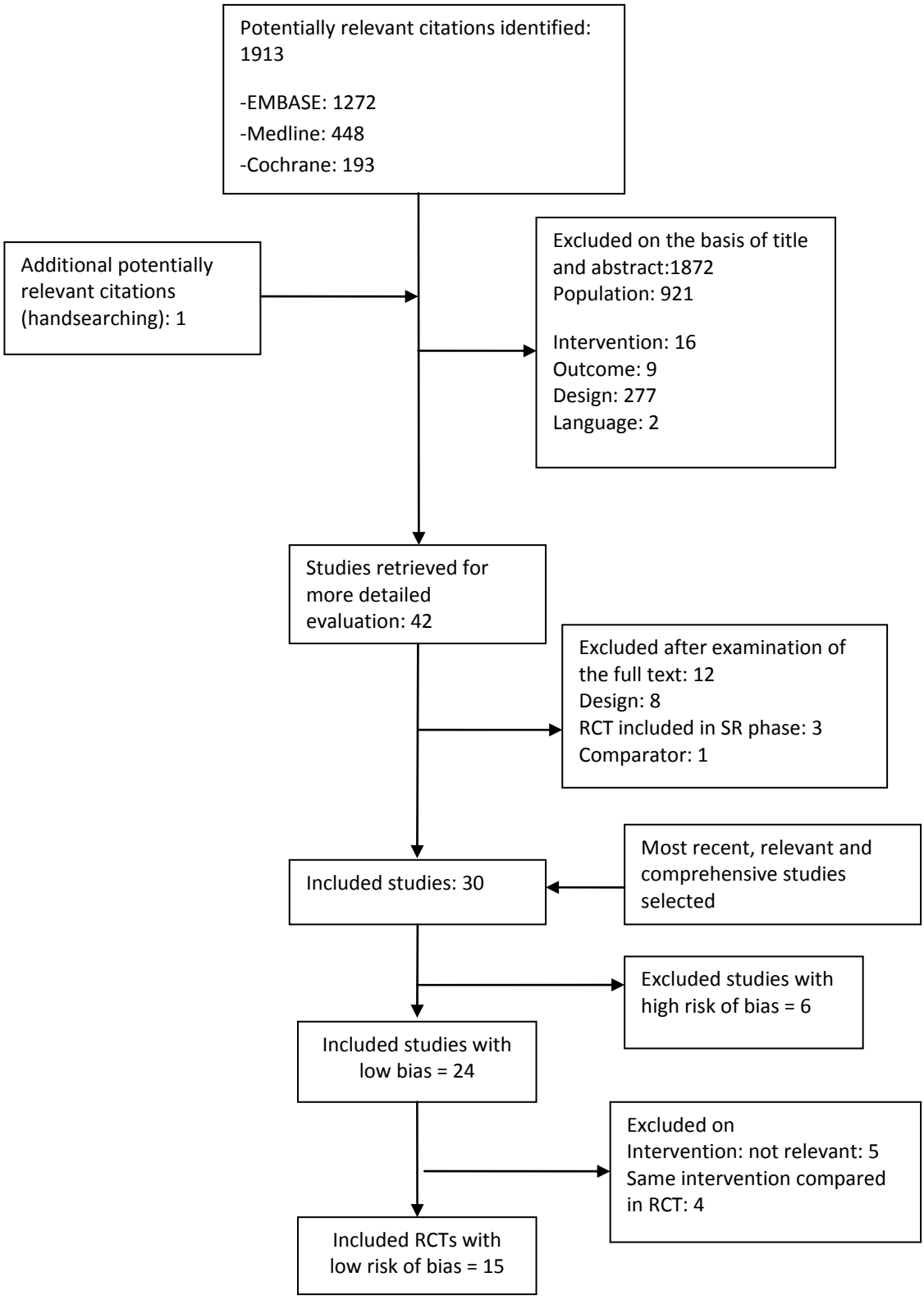
4.1.2.3 Final selection: 15 relevant RCTs

However nine of the 24 RCTs were further excluded as the interventions were not relevant for this review:

- Two RCTs [97 98] evaluated the surgical technique CHIVA, a procedure not currently used in Belgium;
- Three RCTs [91 100] evaluated the technique of cryostripping, also not currently used in Belgium;
- Four other RCTs [79 80 84 87]had treatment arms that compared the same intervention; making the evidence for treatment difference not possible.
  - Blaise et al. (2010)[79] and Hamel-Desnos et al. (2008)[87] compared 1% vs 3% polidocanol foam use in sclerotherapy;
  - Doganci et al.[84] compared the 980 nm laser and bar-tip fibre with 1470 nm laser and radial fibre (EVLT trial);
  - Carradice et al. (2009)[80] compared EVLT and EVLT combined with phlebectomy.

Finally, 15 RCTs were included. The figure below shows the flow of studies in the review.

Figure 4. Results of searches and selection of RCTs



4.2 OVERVIEW OF INCLUDED SYSTEMATIC REVIEWS

Table 3 is an overview of the 22 included systematic reviews.

Table 3. Overview of the 22 relevant systematic reviews evaluating treatments for varicose veins

Intervention	Reference	Number
Multiple treatments	Rees 2009, Brar 2010, Leopardi 2009, Van den Bos 2009, Luebke 2008, ASERNIP 2008 [29 36 56-59]	6
EVLT	MSAC 2008, Ontario health technology assessment 2010, CADTH 2010, HAS 2008,[33 64-66]	4
RFA	Adi 2004, NICE 2003, Luebke 2008, HAS 2008 [34 67 68 69]	4
Sclerotherapy	Hamel-Desnos 2009, NICE 2009, Jia 2007, Tisi 2006, Alberta Heritage for Medical Research 2004[35 60-63]	5
Surgery	Rigby 2004 [30]	1
Drugs	Martinez 2005 [37]	1
Compression Hosiery	Palfreyman 2009 [70]	1

Two limitations have been noted by the authors of the systematic reviews:

- firstly, there is limited long term data on recurrence rates for the new techniques, making comparison with surgery (for which there is longer-term data available) difficult,
- secondly, many studies did not uniformly report or use the CEAP classification, making it difficult to compare patient populations between the studies and to precise the clinical effect of the treatment.

4.2.1 Systematic reviews on multiple treatments

Six systematic reviews on multiple treatments were identified (see appendix 9.4.1) [29 36 56-59]. There was a large amount of overlap of included RCTs amongst these reviews. Rees et al., 2009[29] is a recent National Health Service (NHS) review that included more RCTs than the other identified reviews. This systematic review was selected as the most recent and comprehensive one with a low risk of bias: it will be discussed in more detail in the next section.

4.2.1.1 NHS review on laser therapy, RFA and sclerotherapy interventions

The evidence review conducted by the Rees et al. has been set out to evaluate the efficacy, safety and cost-effectiveness of all endovascular techniques employed in the UK[29]. Studies were included if they compared standard treatment of varicose veins or no treatment with one or more minimally invasive techniques (RFA, EVLT, sclerotherapy), or if they compared two or more of the minimally invasive techniques.

Reference checking against this NHS review [29] was carried out in comparison with all other selected systematic reviews to ensure all relevant RCTs on radiofrequency, laser treatment therapy and sclerotherapy were included.

- RFA: the NHS review included all the RCTs from the other RFA reviews;
- Sclerotherapy: the NHS review identified six RCTs investigating sclerotherapy. These were also the major RCTs in the other sclerotherapy reviews but five additional RCTs were included by other authors: Hamel-Desnos et al., 2003[101], Rabe et al., 2008[92], Ouvry et al., 2008[90], Rao et al., 2005[102], Alos et al., 2006[103].
- EVLT: Rees et al., 2009[29] included four RCTs that were commonly included in the other EVLT reviews. However a more recent review from Ontario identified two additional RCTs by Disselhoff et al.[82] and Theivacumar et al.[104].

The evidence from the 14 RCTs included by Rees et al. will be summarised in each paragraph describing the corresponding intervention.

4.2.1.2 Other systematic reviews on multiple treatments

Two good quality reviews, ASERNIP, 2009[58] and Leopardi et al., 2009[57] contain duplicate data, as Leopardi et al. is a publication of the ASERNIP report.

Van den Bos et al., 2009[59] and Luebke et al. (2008)[36] carried out meta-analyses of different study types, which limits the validity of their analyses.

Brar et al., 2010[56] was limited by a small number of RCTs with short-term follow-up.

4.2.2 Endovenous laser therapy

Four reviews with a low risk of bias were selected (see appendix 9.4.2) [33 64-66].

The most recent and comprehensive one was an Ontario Health Technology Assessment series[64]. This report provided evidence on EVLT compared with surgery and with the minor comparators foam sclerotherapy and RFA. It includes RCTs evaluated in the other three systematic reviews [33 65 66]. The review from the Haute Autorité de Santé[66] includes one additional RCT[105].

4.2.3 Radiofrequency ablation

Four systematic reviews studied RFA (see appendix 9.4.4)[34 67-69]. These reviews contain the same small number of available RCTs, all included as well in the Rees et al. review[29].

4.2.4 Sclerotherapy

Five systematic reviews with a low risk of bias were included (see appendix 9.4.6) [35 60-63]. The same trials were included in different reviews.

- Hamel-Desnos et al., 2009[60], compared liquid versus foam sclerotherapy.
- The recent NICE guidance[61] and Jia et al. (2007)[35] evaluated foam sclerotherapy.
- Tisi et al., 2006 [62] reviewed the evidence on sclerotherapy in general.
- An HTA from Alberta published in 2004[63] included five RCTs.

4.2.5 Surgery

Surgical interventions were studied in the context of comparators in reviews on EVLT, sclerotherapy and RFA. A Cochrane review by Rigby et al, 2004[30] compared surgery with sclerotherapy (see appendix 9.4.8). However the RCTs have been superseded by more recent studies included in the Rees review[29].

4.2.6 Compression hosiery

Compression hosiery is not covered by Rees et al.[29] but analysed in a separate systematic review with a low risk of bias [70](see appendix 9.4.9).

4.2.7 Drugs

One Cochrane review analysed the use of medications for the treatment of chronic venous insufficiency (see appendix 9.4.10)[37].

4.3 OVERVIEW OF INCLUDED RCTS

Table 4 summarises the 15 included RCTs. These will be discussed in more detail under each treatment heading in the results by intervention section.

Most RCTs analysed RFA and EVLT interventions, with many trials comparing these procedures with surgery. Patient numbers ranged from 43 to 280. The majority of trials were conducted in hospitals and four trials reported on patients treated in outpatient clinics [85 90 92 96]. The overall patient follow-up times were generally low with two years being the longest follow-up.

All patients included in the trials had varicose veins of the GSV, with the exception of the RCT evaluating drug therapy[37]. The CEAP classification (see table 5) was reported in all RCTs with most patients (>70%) classified C2 or C3.

Table 4 Overview of RCTs evaluating treatments for varicose veins

Intervention	Reference	Number
RFA versus EVLT	Almeida 2009 78,Goode 201088, Shepherd 201094	3
RFA versus surgery	Subramonia 2010 95 Helmy Elkaffas 2011 99	2
EVLT versus surgery	Carradice 201171, Christenson 201081, Pronk 201096, Rasmussen 201093	4
EVLT versus EVLT/ligation of SFJ (mixed treatment)	Disselhoff 2008b 82	1
Sclerotherapy (foam versus liquid)	Ouvry 200890, Rabe 2008 92	2
Sclerotherapy (foam) versus surgery	Figueiredo 200985	1
Compression hosiery	Houtermans-Auckel 200986	1
Drugs	Martinez-Zapata 200889	1

Table 5. CEAP classification of patients in the included RCTs

Intervention	Reference	CEAP
RFA versus EVLT	Almeida 2009[78]	C2 >87%
	Goode 2010[88]	C2-6
	Shepherd 2010[94]	C1-2 37% C3-4 57% C5-6 6%
RFA versus surgery	Subramonia 2010[95]	C2 79 % C3 18% C4-6 3%
	Helmy Elkaffas 2011[99]	C2 53% C3 30% C4 12% C5 5%
EVLT versus surgery	Carradice 2011[71],	C2-70% C3-6 30%
	Christenson 2010[81],	C2-6
	Pronk 2010[96],	≥2
	Rasmussen 2010[93]	C2-4
EVLT versus EVLT/ligation of SFJ (mixed treatment)	Disselhoff 2008b[82]	C2
Sclerotherapy (foam versus liquid)	Ouvry 2008[90]	C2-6
	Rabe 2008[92]	C2 44% C3 28% C4 19% C5 5%
Sclerotherapy (foam) versus surgery	Figueiredo 2009[85]	C5 – healed venous ulcers
Compression hosiery	Houtermans-Auckel 2009 [86]	C2-3
Drugs	Martinez-Zapata 2008 [89]	C1-6

5 RESULTS BY INTERVENTION

5.1 ENDOVENOUS LASER THERAPY

5.1.1 Results from systematic reviews

The NHS review from Rees[29] included four RCTs evaluating endovenous laser therapy (EVLT)[93 106-108]. All studies compared EVLT (with SFJ ligation) with surgery, SFV ligation and stripping. One study [108] enrolled patients with bilateral GSV varices and compared the techniques between the two legs. Follow-up periods were short, ranging from 16 weeks [106] to one year [107].

Patient satisfaction with the procedure was similar for both treatments across the four studies. In the study comparing treatment between each leg, 70 per cent of patients preferred the laser side (p=0.018)[108]. Likewise, pain scores were similar except in one trial, where higher post-operative pain was recorded in the surgery group[109].

Return to daily activities was faster for the EVLT group (two days versus seven days, p=0.001) in the Darwood et al., 2008 trial[107]. Conversely, Kalteis et al., 2008 [106] found that the surgery patients returned to work sooner than the EVLT patients (14 days versus 20 days, p=0.054) although the EVLT patients in this trial had SFJ ligation as well, and 48% of EVLT patients underwent general anaesthesia compared with 34% in the surgery arm. However, the use of return to work is a poor outcome measure, given its dependency on the social security system.

Overall, surgery was found to cause more oedema and bruising than EVLT. Post-operative infections were reported in the surgery group in two of the studies[106 107]. Phlebitis was more commonly reported in the EVLT group[107]. Skin burns and nerve damage were rare complications of EVLT.

Efficacy outcomes were most commonly reported as occlusion rate after the procedure. All studies reported an occlusion rate in both treatment arms greater than 94% with follow-up of this outcome ranging from 30 days to 6 months Two RCTs [106 107] reported similar efficacy outcomes for EVLT and surgery as judged by post-operative assessment with colour duplex ultrasound and clinical assessment.

5.1.2 Results from randomised controlled trials

Eight RCTs evaluating EVLT were found.

- Three RCTs comparing EVLT to RFA (see RFA section) [78, 88, 94];
- Four RCTs comparing EVLT with surgery[71 81 93 96];
- One RCT comparing EVLT with a mixed intervention (EVLT and ligation of the SFJ)[82].

Two ongoing trials were identified from the clinicaltrials.gov search: a Swedish study (NCT00621062) comparing EVLT, RFA and sclerotherapy with surgery and a study (NCT00529672) from The Netherlands comparing EVLT and sclerotherapy with surgery.

5.1.2.1 EVLT versus surgery (4 RCTs)

Efficacy

The efficacy outcome was reported in three of the four RCTs[81 93 96] i.e. recurrence of GSV at one or two year follow-up through DUS scan. Recurrence of varicose veins was similar for EVLT and surgery:

- Pronk et al. (2010) reported no significant difference in the development of recurrent varicose veins at 1 year (10% for surgery and 9% for EVLT)[96];
- At 2 year follow-up, Christenson et al. (2010) found 7 of 98 limbs had re-opened compared with none in the surgical group but this result was not significant[81];
- The Rasmussen trial did not report any difference in clinical recurrence rates between EVLT (26%) and surgery (37%) groups after 2 years[93].

Quality of life

In the four RCTs comparing EVLT to surgery, the improvement of quality of life was similar between groups at final study follow-up. The study by Carradice et al. (2011) comprehensively assessed quality of life outcomes using the UK SF-36 V1, EQ-5D and AVVQ tools. The patients in the surgical arm experienced a significant decline in 5 of 8 SF-36 domains ($p < 0.001$ to $p=0.049$) due to increased pain and disability, whereas the patients in the EVLT arm had deterioration in only two domains. From four weeks post-procedure there were no differences between the groups[71].

Pain

EVLT was associated with less pain post-procedure, with the exception of the Pronk et al. trial (2010) whose EVLT patient's experienced higher pain scores at day 7 ($p < 0.01$) and day 14 ($p < 0.01$)[96]. However, this study used an older laser than the technologies currently used.

Complications

Carradice et al (2011)[71] reported post operative complications in surgery (n=133) and EVLT (n=137) patients. In this study, patients receiving surgery experienced higher rates of sensory disturbance, (surgery n=13 versus EVLT n=4, p=0.02) haematoma (surgery n=11 versus EVLT n=1, p=0.003) and infection (surgery n=8 versus EVLT n=2, p=0.048)[71]. Bruising was more common after EVLT[81].

Return to normal activities

Return to normal activities was similar between groups in the RCTs reporting this outcome [81 96] with the exception of the Carradice trial where the surgical patients took longer to return to normal activities (median 14 days versus 3 days; $p < 0.001$)[71].

5.1.2.2 EVLT versus ligation of the SFJ (1 RCT)

Efficacy

One RCT evaluated ligation of the SFJ after EVLT using an EVLT comparator group. This trial randomised 43 patients with bilateral varicose veins with SFJ incompetence and GSV reflux from the groin to below the knee. The study found no difference between the groups with respect to varicose vein recurrence measured by DUS at 2 year follow-up[82].

Complications

Disselhoff et al., 2008, found no significant difference between the groups with respect to bruising, pain score, tightness along the GSV and superficial thrombophlebitis. No patient had a skin burn or a major complication[82].

5.1.3 Summary: Endovenous Laser Therapy

- **There is evidence of moderate quality for a similar clinical efficacy of EVLT and surgery;**
- **The included studies provided a follow-up of up to two years;**
- **There is low quality of evidence that surgery was associated with more post-operative pain, haematomas and infections;**
- **Pain and bruising were the most commonly reported side-effects of EVLT; hematoma, infections, phlebitis, sensory disturbances were also possible complications.**

5.2 RADIOFREQUENCY ABLATION

5.2.1 Results from systematic reviews

The NHS review from Rees[29] included four RCTs comparing radiofrequency ablation (RFA) with surgery[110-113].

As with the EVLT trials, the study populations were small (15 to 40 patients). The longest follow-up period for clinical outcomes was one year [113]. One study on 16 patients compared pain and bruising in 16 patients with bilateral recurrent long saphenous varicose veins (endoluminal thermal ablation on one leg versus classical surgery on the other leg)[110].

Mean treatment time for RFA was found to be shorter than surgery in two trials [110 111] and longer than surgery in the other two studies [112 113]. However, the current designs of RFA are faster than the RFA devices used in these studies.

At short term RFA performed better than surgery with regards to a faster return to work, less pain associated with the procedure, less bruising and haematomas[110-113].

In the EVOLVeS study, patient-reported quality of life scores favoured RFA at 3 days and 1 week post procedure ($p < 0.001$), however by four months the difference in quality of life scores was negligible[111].

Studies with longer follow-ups found that RFA patients were more satisfied with the procedure ($p < 0.001$) and cosmetic outcome ($p=0.006$) at one year[113]. Lurie et al. also found that the RFA group scored better than the surgery group at 1 and 2 years[114].

Similar occlusion rates (> 95%) were reported for RFA and surgery post-procedure[111,112]. Stotter 2006[113] reported that two patients out of 20 in the RFA group had segmental recanalisation < 10 cm at one year. The EVOLVeS follow-up study[114] found cumulative recurrence rates for varicose veins of 14% for RFA and 21% for surgery, but statistical significance was not reached.

5.2.2 Results from randomised controlled trials

Five RCTs evaluating RFA were identified.

Three compared RFA with EVLT [78 88 94]

Two compared RFA with surgery [95 99].

5.2.2.1 RFA versus EVLT (3 RCTs)

Efficacy

Similar rates of occlusion between RFA and EVLT were reported at 6 months by DUS in one trial[88]. The other two RFA versus EVLT trials had short follow-up periods and did not report efficacy as they were designed to measure differences in pain, complications and QoL outcomes [78 94].

Quality of life

Quality of life measurements were recorded in the three trials comparing RFA to EVLT. The trial by Almeida et al. (2009) reported that the changes in global QoL scores (CIVIQ tool) were significantly higher with RFA treatment at day 7 and day 14 after treatment compared with the EVLT arm[78]. The other two trials found no significant difference in QoL scores between the treatment groups88 94.

Pain

In the trials comparing RFA with EVLT, RFA (Closure FAST) patients reported significantly lower pain levels than the EVLT group at 48 hours (0.7 versus 1.9), 1 week (0.2 versus 1.8) and 2 weeks (0.2 versus 1.2); $p < 0.00178$. Similar results were reported in the other two RCTs showing RFA to be associated with less pain up to 11 days post procedure88 94.

Complications

The Almeida et al. (2009)[78] trial found that minor complications were more prevalent in the EVLT group than the RFA group (22% versus 4.4%, p=0.0210). They also reported significantly greater overall rates of phlebitis in EVLT patients compared with RFA patients (14.6% versus 0%, p=0.009), and significantly greater rates of erythema in EVLT compared with RFA (9.8% versus 0%, p=0.045).

However the Shepherd at al. (2010) trial found similar rates of complications across the groups. One patient in the RFA group suffered a pulmonary embolus 2 weeks post-procedure[94].

5.2.2.2 RFA versus surgery (2 RCTs)

Efficacy

Only one of the two trials[95, 99] that compared RFA to surgery reported efficacy results. This study showed a primary occlusion rate of 94% for RFA and 100% for surgery assessed by DUS over a follow-up range of six to 20 months[99].

Quality of life and patient satisfaction

The trial by Subramonia and Lees (2010) showed that RFA performed significantly better than conventional surgery in the short term outcomes of patient satisfaction, quality of life improvement and pain. In this trial all patients received a general anaesthetic.

Pain

One RCT reported (n=88) that postoperative pain scores in the first week post-procedure favoured RFA over surgery (1.70 versus 4.00; p=0.001)[95].

Complications

A high rate of severe haematomas (n=30), three cases of serious infections and one deep venous thrombosis occurred in the surgical group (n=90) of the Helmy ElKaffas et al. (2011)[99] trial. In the RFA group, one patient had a severe haematoma and 6 developed thrombophlebitis in the postoperative period.

Other outcomes

Patients in the RFA group returned to normal activities quicker than the surgical group (2 days versus 10 days; $p < 0.001$). Theatre time and procedure time were both significantly shorter in the surgical group[95].

5.2.3 Summary: Radiofrequency ablation

- **There is moderate quality of evidence for a similar clinical efficacy of RFA and EVLT, also for RFA and surgery;**
- **Low patient numbers and short follow-up (maximum one year) have to be taken into consideration in the interpretation of the results of studies evaluating RFA;**
- **Pain and bruising were the common reported side-effects of RFA; hematoma and infections were also possible complications.**
- **Evidence of low quality suggests that RFA performs better than surgery and EVLT with regards to post-procedure pain. RFA was also reported as superior to surgery for the other post-procedural complications and quality of life.**

5.3 SCLEROTHERAPY

5.3.1 Results from systematic reviews

Five RCTs (6 publications) were included in the NHS review[11 29 115-119] from Rees et al. Trials included larger populations than for the previously discussed techniques (patient groups > 30 patients).

Three RCTs (four publications) evaluated liquid sclerotherapy[11, 115-117]: the longest follow-up was ten years. Overall the recurrence of varicose veins varied between one third of the patients (for surgery combined with sclerotherapy) and half of the patients (for sclerotherapy). The other two trials evaluated foam sclerotherapy and had follow-up periods of up to one year[118, 119].

Surgery had better or similar efficacy outcomes (occlusion rates) compared with sclerotherapy. Wright et al. (2006)[119] was the only RCT to directly compare liquid with foam sclerotherapy. The foam product Varisolve® outperformed standard sclerotherapy based on occlusion rates at 12 months (foam 89% versus liquid 76% $p < 0.001$).

The RCTs included in the SRs also highlight the adverse effects linked to the procedure. Adverse events associated with sclerotherapy include skin pigmentation (6%) and thrombophlebitis (3/30 patients)[118]. Furthermore Wright et al. described six reports of transient neurological symptoms and 11 occurrences of deep vein thromboses associated with the foam product Varisolve®. These side effects diminished when the dose was reduced from 60 ml to 30 ml[119].

Return to work was quicker after foam sclerotherapy compared with surgery[118, 119] and patients undergoing surgery reported more pain than those in the sclerotherapy group[119].

5.3.2 Results from randomised controlled trials

Three RCTs evaluating sclerotherapy were included:

- Two comparing liquid versus foam sclerotherapy[90, 92]
- One comparing the procedure to surgery[85].

These trials were limited by low patient numbers (56 to 108) and short follow-up periods (3 months to 2 years).

An ongoing RCT (NCT01103258) conducted by the Maastricht University Medical Center was identified on www.clinicaltrials.gov. This study is comparing the effects, costs and patient preferences between foam sclerotherapy and surgery in the treatment of greater varicose veins.

5.3.2.1 Liquid sclerotherapy versus foam sclerotherapy (2 RCTs)

Efficacy

No RCTs measured clinical outcomes (CEAP classification): both RCTs evaluated the efficacy of the interventions based on the results of Doppler-ultrasound.

In the first trial from Rabe et al. (2008) elimination of reflux was more successful in the foam group (69%) compared with the liquid group (27%) ($p < 0.0001$)[92] at three months.

In the second trial from Ouvry et al. (2008), at three weeks post-intervention, similar efficacy results were seen (85% foam versus 35% liquid; $p < 0.001$)[90]. At two year follow-up, these rates had dropped to 12% in the liquid group (4 patients) and 53% in the foam group (25 patients) but these results are based on low patient numbers due to high drop-out rates[90].

Quality of life and patient satisfaction

Quality of life data was lacking in these trials. Rabe et al. (2008) found that patient satisfaction was significantly higher in the foam group compared with the liquid group[92].

Complications

There was no difference in the adverse event data between the groups[92]. Adverse events most commonly reported for sclerotherapy included pain, haematoma, phlebitis/thrombophlebitis and pigmentation or hyperpigmentation.

5.3.2.2 Foam sclerotherapy versus surgery (1 RCT)

Efficacy

At 180 day follow-up in the foam sclerotherapy compared with surgery trial, 90% of foam sclerotherapy patients had saphenous vein obliteration compared with 78% in the surgery group with a non-significant difference between the two methods[85].

Complications

There was no difference in the adverse event data between the groups. The most frequent complications were suture dehiscence in the surgery group and thrombus not requiring drainage in the sclerotherapy group[85].

5.3.3 Summary: Sclerotherapy

- **The advantage of sclerotherapy is that no anaesthesia is required;**
- **The studies provided a follow-up to two years for foam sclerotherapy and to 10 years for liquid sclerotherapy;**
- **There is evidence of moderate quality to support a similar efficacy (occlusion rates) of foam sclerotherapy, liquid sclerotherapy and surgery with follow-ups to 2 years but there are few data on clinical efficacy;**
- **Evidence of low quality suggests that surgery performs better than liquid sclerotherapy at 10 years;**
- **Adverse events reported for sclerotherapy included pain, haematoma, phlebitis/thrombophlebitis, thrombosis, transient neurological symptoms and pigmentation.**

5.4 SURGERY

The majority of the evidence on varicose vein surgery has already been discussed in the sections above since in the Rees review[29], the included RCTs compared sclerotherapy, RFA and EVLT with surgery. Pain, paraesthesia due to saphenous nerve injury, haematoma and bruising are possible complications.

In addition to this evidence, one Cochrane review[30] published in 2004 compared surgery with liquid sclerotherapy: sclerotherapy was more effective in the first year but at five years surgery was the most effective intervention. Evidence from this review is also covered in the Rees review[29].

No additional RCTs specifically evaluating surgery were identified.

Summary: surgery

Surgery has been the comparator in most studies on new endovenous techniques.

- **The new techniques usually perform better at the short term in terms of lower rates of complications and faster return to work;**
- **The efficacy after a few months is similar between surgery and the other techniques;**
- **Surgery seems more effective than liquid sclerotherapy in the few studies with follow-ups longer than 5 years;**
- **Pain, paresthesia, haematoma, bruising and infections are possible complications.**

5.5 COMPRESSION HOSIERY

The conclusion of one systematic review on this topic was a limited evidence for effectiveness for varicose veins[70]. Hosiery was classified on the basis of pressure applied just above the ankle with the use of inelasticated socks, stockings and tights, in either thigh or knee length. Patient populations varied between the included studies with many studies enrolling any patient with chronic venous insufficiency (CVI) rather than varicose vein patients only. The evidence was based on 25 studies; however 11 of these were non-randomised studies and the majority of the 10 included RCTs were of poor methodological quality with a short follow-up.

Compression stockings reduced pain and improved leg symptoms but no RCTs reported on outcomes directly evaluating the slowing or preventing the occurrence of varicose veins. Overall, it is difficult to make any judgement on the effectiveness of compression bandages from this review due to the lack of robust, adequately-powered RCTs reporting relevant efficacy outcomes.

No additional RCT was found for the use of compression stockings for the treatment of varicose veins.

Summary: compression hosiery

There is low quality of evidence that compression hosiery is effective for improving the symptoms of varicose veins.

5.6 DRUGS

5.6.1 One Cochrane review on the effect of phlebotonics for chronic venous insufficiency

One Cochrane review (with database searches from 2005) has evaluated the use of oral phlebotonics for the treatment of chronic venous insufficiency (CVI)[37]. No paper has been found on the effect of these medications on varicose veins specifically.

Fifty-nine RCTs were included in this review. They assessed the use of these drugs to improve the outcomes of oedema, venous ulcers, trophic disorders and subjective symptoms. This Cochrane review did not find evidence supporting the use of phlebotonics for CVI. The included RCTs in this review had several overall limitations. Firstly, diagnosis criteria and CVI definitions were often not used or reported, making the study populations heterogeneous. Secondly, the study outcomes were not well reported in the studies. The results were not separated into the different stages of CVI which meant interpretation on the use of drugs for the treatment of varicose veins was limited.

5.6.2 Lack of evidence in one RCT

One RCT supported by the industry studied 509 patients with chronic venous disease randomised to calcium dobesilate or placebo during 3 months. This trial found no significant difference between the groups for the main outcomes i.e. QoL, oedema and symptoms after three months. A significant overall improvement in QoL in both groups suggested a placebo effect[89]. An improvement in QoL was observed 9 months after the end of the treatment but this observation was based on a secondary analysis.

Summary: drugs

The studies on medications targeted chronic venous disease patient population rather than varicose vein patients specifically. Overall there is no evidence to support the effectiveness of phlebotonics.

5.7 OTHER CONSERVATIVE TREATMENTS

No systematic reviews or RCTs on other conservative treatments, such as exercise and weight loss for the treatment of varicose veins, were identified.

6 SAFETY CONSIDERATIONS

Complications and post-procedural adverse events have been reported where data was available in the included SRs and RCTs described above. However, the RCTs were poorly designed to identify possible complications, in particular due to their small sample size. As a consequence, non-RCTs reporting on safety outcomes were identified from the database search to supplement the safety data.

This section provides an overall summary of the safety findings from the included SR and RCTs and relevant non-RCT studies reporting on the safety aspects of the interventions (see details in appendix 9.7).

6.1 ENDOVENOUS LASER THERAPY

Adverse events reported from included studies in section 5.1 were:

- pain
- bruising
- haematoma
- thermal injury
- hyperpigmentation
- thrombophlebitis / risk of deep venous thrombosis
- temporary paraesthesia

Similar adverse events were found in the additional publications that reported on safety outcomes.

- A systematic review of EVLT induced complications by Van Den Bos et al. (2009) concluded that ecchymoses and pain are frequently reported whereas nerve injury, skin burns, deep venous thrombosis and pulmonary embolism rarely occur (< 1%)[54].
- A large cohort study of 1985 EVLT ablations report similar complications and this study also reported two cases (0.13%) of deep venous thrombosis[120].
- A smaller cohort study of 150 patients reported two patients with sural nerve paraesthesia and six patients with superficial thrombophlebitis[121].
- A prospective single arm non-RCT by Rathod et al. (2010)[122] studied the use of a higher wavelength of 1470-nm and reported similar safety data to the EVLT study[121] described above. Additionally, the authors reported a dose-dependent relationship for the paraesthesia rate; with a significantly greater (p=0.009) paraesthesia rate in those exposed to a greater energy density (greater than 100 J/cm).

6.2 RADIOFREQUENCY ABLATION

Adverse events reported from included studies in section 5.2 were:

- pain
- bruising
- haematoma
- Thermal injury
- thrombophlebitis / risk of deep venous thrombosis
- temporary paraesthesia

A prospective case series of 225 patients (295 limbs) reported similar adverse events: haematomas (1.4%), ecchymoses (5.8%) paraesthesia (3.4%) and pigmentations (3.1%) being the most common side effects[123].

6.3 SCLEROTHERAPY

Adverse events reported from included studies in section 5.3 were:

- tissue necrosis
- skin staining/ pigmentation
- matting (formation of microtelangiectasias)
- induration
- risk of deep venous thrombosis

A large prospective, multicentre, controlled study enrolled 1025 patients undergoing foam sclerotherapy. This study reported one case of septicaemia, one transient ischemic attack and 11 venous thromboembolic events (including one pulmonary embolism)[124].

A RCT compared sclerotherapy foam concentrations (1% versus 3% polidocanol sclerosant foam) in 143 patients. At 3 years the incidence of local side effects (pigmentation and matting) did not significantly differ between groups (6% and 9% respectively)[79].

A review by Guex et al. summarised the complications of sclerotherapy, based on the literature and on a French registry[125]. The estimates of the incidence of complications were higher for foam sclerotherapy (0.58%) than for liquid sclerotherapy (0.55%). Matting and residual pigmentations are common (1% to 10%) for foam sclerotherapy and uncommon (0.1% to 1%) for liquid sclerotherapy. Among the most serious complications, deep venous complications after foam sclerotherapy is the most frequent one with an estimated range between 0.09% and 0.2% in the French Registry (n=12173 sessions)[125]. Deep venous complications and large skin and muscular necrosis are also mentioned for liquid sclerotherapy but less frequently reported (<0.01%). Other serious complications are isolated case reports.

Cases of stroke (n=2) and transient ischemic attacks (n=3) have also been reported in the literature analysed by Guex et al. after foam and liquid sclerotherapy [125]. Another case study describes three cases of stroke after foam sclerotherapy: they were all found to have a patent foramen ovale[126].

6.4 SURGERY

Adverse events reported from included studies in section 5.4 were:

- pain
- cutaneous nerve injury
- wound infection
- haematoma
- risk of deep venous thrombosis

Bleeding due to vascular injury is also a serious complication of varicose vein surgery. A qualitative systematic review by Rudström et al. (2007) estimated the incidence of vascular injuries in varicose vein surgery to be low (0.0017% - 0.3%); however the authors concluded that an accurate estimate is difficult due to the lack of epidemiological studies[127].

A long-term complication is the recurrence of varicose veins (20% to 50% of cases) resulting from neovascularisation at the previously ligated SFJ. Common use of colour duplex scanning since the 1990s has demonstrated neovascularisation results from angiogenesis with new vessel formation from the exposure of the SFJ stump endothelium [128, 129]. In an effort to limit neovascularisation, clinicians have developed surgical techniques to invert the SFJ stump with limited success[129] or prosthetic barriers such as a patch over the stump shows more promising results[128].

6.5 SUMMARY: SAFETY

- **Pain, bruising and haematomas are complications common to all procedures;**
- **Some studies show that EVLT, RFA and sclerotherapy result in less bruising, haematoma and post-procedural infections than surgery;**
- **Specific complications have been more frequently described for EVLT (pigmentation) and foam sclerotherapy (matting, pigmentation, thromboembolic events);**
- **Cases of serious complications (e.g. thrombophlebitis, deep venous thrombosis) have been reported; however the included studies were not designed to find differences in adverse events between the procedures;**
- **Finally, it should be noted that long-term complications and recurrence rates remain unknown for the most recent techniques, in particular foam sclerotherapy.**

7 ANAESTHESIA

An additional literature search using anaesthesia search terms combined with varicose vein or intervention terms did not reveal any additional relevant publications. Any information on anaesthetic use was collected from the included studies (SR and RCTs) to evaluate the evidence on what type of anaesthetic is most appropriate for each intervention.

One recent and relevant Canadian HTA was identified: "Anaesthesia for venous stripping and ligation procedures: clinical effectiveness, safety, cost-effectiveness and guidelines". This review included six SRs and three RCTs already included in this review. They also added one economic evaluation and three non-RCTs[65].

7.1 DESCRIPTION OF ANAESTHESIA IN THE INCLUDED RCTS

The type of anaesthesia was usually reported in the methods of the RCTs but not in the results. This means that further interpretation on patient outcomes by anaesthetic type was not possible. The use of each anaesthetic type when reported in the included RCTs is summarised below:

- Endovenous laser therapy:
  - general or spinal anaesthesia[81 82];
  - general anaesthesia[88 94];
  - local tumescent anaesthesia[71 78 82 93 96].
- Radiofrequency ablation:
  - general anaesthesia[88 94 95];
  - regional anaesthesia [85];
  - local tumescent anaesthesia[78 99].
- Surgical stripping:
  - general anaesthesia[71 95 99];
  - general or spinal anaesthesia [81 82]
  - regional anaesthesia [85];
  - local tumescent anaesthesia[93];
- Sclerotherapy: no anaesthesia[85 90 92].

7.2 ANAESTHESIA SUMMARY

There is a lack of studies directly comparing anaesthetic procedures:

- General anaesthesia is the most commonly used anaesthesia in the surgical treatment of varicose veins (stripping);
- The new endovenous treatments, in particular laser therapy, are routinely performed under tumescent local anaesthesia;
- Sclerotherapy requires no anaesthesia.

Table 6. Type of anaesthesia per intervention as reported in the studies

	EVLT	RFA	Sclerotherapy	Surgery
General	+	+		+
Spinal	+	+		+
Local tumescent	+	+		+
No			+	

There is a lack of studies directly comparing anaesthetic procedures:

- **general and spinal anaesthesia are the most commonly used anaesthesia in the studies on surgical treatment of varicose veins;**
- **new endovenous (EVLT, RFA) interventions are also routinely performed under local tumescent anaesthesia;**
- **sclerotherapy has the advantage of requiring no anaesthesia.**

There is no evidence that different anaesthesia techniques influence interventional outcomes.

8 SUMMARY OF FINDINGS AND DISCUSSION

This systematic review addresses the effectiveness and safety of the procedures used to diagnose and treat varicose veins as well as the most appropriate use of anaesthesia for each procedure.

8.1 SUMMARY OF FINDINGS

8.1.1 Diagnostic: duplex ultrasound is the standard procedure

One study confirms the role of duplex ultrasound bef0ore surgical treatment: recurrences and reoperations are less frequent if the intervention is based on this diagnostic procedure rather than on clinical grounds only. A 7 year follow-up (published in 2011) of these patients confirms these results[130].

No evidence was found about other procedures that would provide additional information to the one from duplex ultrasound.

8.1.2 Treatment options: comparable efficacy and complications

8.1.2.1 Similar efficacy between treatment options after several months

All treatment options appear to have similar efficacy outcomes up to two years after the intervention. Most results apply to mild to moderate varicose vein disease (C2 and C3) so it is not possible to summarise the best treatment according to severity. In the same way there is no evidence to support the simultaneous use of invasive procedures on the same leg: only a few studies combined sclerotherapy and classic surgery as one intervention.

Sclerotherapy was found to have higher rates of recurrence than surgery after a few years. However the advantage of sclerotherapy is that it does not require anaesthesia and therefore might be suitable for subgroups of people at risk or as an adjunctive procedure to other treatments.

There is evidence of low quality to support the use of compression hosiery and no evidence that drugs are effective in the treatment of varicose veins.

8.1.2.2 New treatments: less post-operative complications but lack of data for longer follow-up periods

Pain, bruising and hematomas were the most frequent complications reported for all procedures. Surgery was associated with more post-operative pain, haematomas and infections (2 to 5%) than the new procedures. Serious complications were rarely reported. New procedures have specific side effects but there is a lack of well conducted studies on this topic.

8.1.3 Heterogenous anaesthetic procedures

There are no studies directly evaluating different anaesthetic procedures for the same intervention. The analysis of the type of anaesthesia used in the studies on the surgical treatment of varicose veins shows that:

- general (and spinal) anaesthesia are frequently used;
- laser and radiofrequency treatments are also routinely performed under local tumescent anaesthesia;
- sclerotherapy does not require any anaesthesia.

8.1.4 Coherence of the results with other recent publications

Two publications published after the search strategy confirm the results of the present report i.e. a similar short-term efficacy between techniques and the lack of knowledge about the complications after endovenous procedures.

- A meta-analysis published by Murad et al.[131] analysed the efficacy and safety of the treatment options for varicose veins. The authors emphasize the low quality of available evidence (small sample sizes, short-term follow-ups, surrogate outcomes). Their review supports the long-term efficacy and safety of surgery. They also conclude that the efficacy and safety of less invasive treatments have been demonstrated at short-term with less pain and complications.
- A large RCT (580 legs) compared endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping[132]. All treatments were efficacious but foam therapy had worse results after one year (control with duplex ultrasound). Return to normal function was quicker with the new therapies (1 or 2 days versus 4 days for stripping). Two patients had major complications: one pulmonary embolus after foam therapy and one deep venous thrombosis after stripping.

8.2 TRANSFERABILITY OF RESULTS TO THE BELGIAN HEALTH CARE SETTING ?

The results of this review raise the question of their transferability to the Belgian health care setting. In Belgium varicose vein procedures are performed in hospital settings (78% in day hospital)[2]: the billing codes for classical surgery do not allow performing this operation in outpatient settings[133]. Multiple treatments are often conducted in a single session, under general or loco-regional anaesthesia.

In other European countries (e.g. The Netherlands) the procedures are predominantly carried out in an outpatient clinic, under local anaesthesia, also by dermatologists or angiologists. Patients may undergo multiple treatment sessions when needed. A recent paper underlines the positive effect of the new endovenous treatments in terms of possibility to move to outpatient settings, with little or no anaesthesia[134]. The question is to know to what extent this revolution is possible in Belgium.

8.3 STRENGTHS AND LIMITATIONS OF THIS SYSTEMATIC REVIEW

8.3.1 Strengths of this review

The strict methodology of this review included a priori-defined inclusion criteria and quality appraisal tools that contributed to the robustness of the conclusions.

Moreover, the involvement of expert clinicians allowed an optimal choice of diagnostic techniques and treatment procedures according to the current practice in Belgium. The interpretation of the results could in the same way be put in perspective. An illustration is the choice of diagnostic techniques and the superiority of the duplex ultrasound scan compared with the hand-held doppler in clinical practice today.

8.3.2 Methodological limitations of the included studies

8.3.2.1 Small sample size and short-term follow-up

A major limitation of this systematic review is the lack of large scale RCTs evaluating the new treatments of varicose veins. The description of complications following these new procedures is therefore based on case reports or studies of low quality. Moreover the efficacy of these techniques over long-term periods is unknown as most follow-ups are shorter than two years.

8.3.2.2 Heterogeneous populations and outcomes

Heterogeneity of the patient populations with respect to severity (C of the CEAP criteria) could be a limiting factor to gain a clear interpretation of the differences in efficacy and complications between the treatments, although the majority of included patients had mild to moderate disease (C2 and C3).

Other limitations of the included RCTs were the difficulty of applying blinding to patients or clinicians, the variability in the reporting of study outcomes or the reporting of study outcomes that were extraneously influenced such as return to work.

8.3.2.3 Different interventions but similar terminology

Different treatment protocols

Interpretation of the differences between the treatment groups in the trials was sometimes difficult as there were variations in the type of anaesthetic used, and the use of adjunctive procedures such as additional phlebectomies or sclerotherapy was not uniform across study populations.

Evolution of technologies

The protocols and devices differed between the studies. Moreover the included studies on treatment procedures used less performing technologies than the ones currently used. This has implications for the implementation of the results.

8.4 SUGGESTIONS FOR FURTHER RESEARCH

This systematic review highlights the need for further research.

- First, large scale studies are needed to evaluate the efficacy at long term of the new procedures, as well as their safety;
- Second, there is a need for studies that analyse the patient's outcomes when the same intervention is performed using different anaesthesia procedures;
- Third, the question of the feasibility of the new procedures in outpatient settings calls for comparisons of interventions in hospitals and in ambulatory settings.

8.5 KEY POINTS OF THE REPORT

The following key points summarize the conclusions of this systematic review on diagnosis and treatment of varicose veins of the legs:

Duplex colour ultrasound is the standard diagnostic procedure for the diagnosis of varicose veins.

There is moderate quality of evidence (RCTs with limitations) for a similar efficacy and safety of:

- **surgery (with long-term follow-up);**
- **endovenous laser therapy, radiofrequency ablation and sclerotherapy (with maximal follow-up of 2 years);**

Surgery and endovenous procedures have common post-operative complications (pain, bruising, haematomas) but:

- **there is low quality of evidence that the endovenous procedures have less post-operative complications than surgery;**
- **some case reports of complications after endovenous procedures (in particular foam sclerotherapy) highlight the need for larger studies.**

The available evidence does not allow to draw conclusions on the most appropriate type of anaesthesia for each procedure:

- **laser and radiofrequency treatments can be performed under local tumescent anaesthesia;**
- **sclerotherapy does not need any anaesthesia.**

There is low quality of evidence that compression hosiery is effective for improving the symptoms of varicose veins.

There is no evidence for the effectiveness of phlebotonics.

This systematic review highlights the need for well conducted trials in several areas: types of anaesthesia, ambulatory versus hospital setting, compression hosiery, large studies with long-term follow-up for the efficacy and safety of the endovenous procedures.

9 APPENDICES

9.1 ADDITIONAL HANDSEARCHING

- Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé
- Agencia de Evaluación de Tecnologias Sanitarias
- Andalusian Agency for Health Technology Assessment
- L'Agenzia nazionale per i servizi sanitari regionali - The Agency for Regional Healthcare
- Agency for Healthcare Research and Quality
- Adelaide Health Technology Assessment
- Agency for Health Technology Assessment in Poland
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
- Galician Agency for Health Technology Assessment
- Canadian Agency for Drugs and Technologies in Health
- Catalan Agency for Health Technology Assessment and Research
- Center for Drug Evaluation
- Comité d Évaluation et de Diffusion des Innovations Technologiques
- Centro Nacional de Excelencia Tecnológica en Salud Reforma
- Committee for New Health Technology Assessment
- Centre for Reviews and Dissemination
- College voor Zorgverzekeringen
- Danish Centre for Evaluation and Health Technology Assessment
- German Agency for HTA at the German Institute for Medical Documentation and Information
- Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia
- Danish Institute for Health Services Research
- Department of Quality and Patient Safety of the Ministry Health of Chile
- Finnish Office for Health Care Technology Assessment
- GÖG - Gesunheit Österreich GmbH
- Gezondheidsraad
- Haute Autorité de Santé
- Health Information and Quality Authority
- Health Services Assessment Collaboration
- Israel Center for Technology Assessment in Health Care
- Institute for Clinical Effectiveness and Health Policy
- Institute of Health Economics
- International Network of Agencies for Health Technology Assessment
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
- Belgian Federal Health Care Knowledge Centre
- Ludwig Boltzmann Institut für Health Technonoly Assessment
- Health Technology Assessment Section, Ministry of Health Malaysia
- Medical Advisory Secretariat
- Medicare Services Advisory Committee
- Medical Technology Unit - Swiss Federal Office of Public Health

- National Coordinating Centre for Health Technology Assessment
- Quality Improvement Scotland
- National Horizon Scanning Center
- Norwegian Knowledge Centre for Health Services
- Basque Office for Health Technology Assessment
- Swedish Council on Technology Assessment in Health Care
- Unidad de evaluacíon Technologias Santarias
- HTA Unit in A.Gemelli University Hospital
- State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania
- VA Technology Assessment Program
- The Medical and Health Research Council of The Netherlands
- Clinical Guidelines / Pyrmont [Australia]: Medical Journal of Australia - 2005
- CMA Infobase / Ottawa [Canada]: Canadian Medical Association (CMA)
- Guidelines / Canberra [Australia]: National Health and Medical Research Council - 2008
- Guidelines and Reports of the New Zealand Guidelines Group / Wellington [New Zealand]: New Zealand Guidelines Group Inc. - 2007
- NHG-richtlijnen / Utrecht [The Netherlands] : Nederlands Huisartsen Genootschap (NHG) - 2008
- NICE guidance / London [UK]: National Institute for Health and Clinical Excellence (NICE) - 2008
- Recommandations professionnelles de la Haute Autorité de Santé (HAS) /paris [France] : Haute Autorité de Santé (HAS) - 2008
- Richtlijnen (CBO) / Utrecht [The Netherlands]: Kwaliteitsinstituut voor de Gezondheidszorg (CBO) - 2008
- SIGN Guidelines / Edinburgh [UK] : Scottish Intercollegiate Guidelines Network (SIGN) - 2001
- National Guideline Clearinghouse/AHRQ [USA]: http://www.guideline.gov/

9.2 DIAGNOSTIC STUDIES: QUALITY APPRAISAL AND DETAILED RESULTS ABOUT THE USE OF HAND-HELD DOPPLER

9.2.1 Quality items derived from QUADAS tool

The following items are assessed using in the QUADAS tool[38]:

1. Was the spectrum of patients representative of the patients who will receive the test in practice? (representative spectrum)
2. Were selection criteria clearly described?
3. Is the reference standard likely to classify the target condition correctly? (acceptable reference standard)
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (acceptable delay between tests)
5. Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? (partial verification avoided)
6. Did patients receive the same reference standard irrespective of the index test result? (differential verification avoided)
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? (incorporation avoided)
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the reference standard results interpreted without knowledge of the results of the index test? (index test results blinded)
11. Were the index test results interpreted without knowledge of the results of the reference standard? (reference standard results blinded)
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (relevant clinical information)
13. Were uninterpretable/ intermediate test results reported? (uninterpretable results reported)
14. Were withdrawals from the study explained? (withdrawals explained)

9.2.2 Quality appraisal of varicose vein diagnostic studies

Item	QUADAS tool questions	Blomgren et al 2005[47π]	Campbell et al. (2005)[135]	Darke et al. (1997)[136]	Daher et al. (2001)[137]	Kambal et al.(2007)[138]	Lee et al. (2008)[48]
1	Pts representative of normal practice?	yes	yes	Yes	yes	yes	yes
2	selection criteria clearly defined?	yes	unclear	Yes	unclear	no	yes
3	Acceptable ref standard?	yes	yes	yes	yes	yes	yes
4	Acceptable delay between tests? †	NA	unclear	yes	unclear	yes	yes
5	Partial verification avoided?	yes	yes	yes	yes	yes	unclear
6	Differential verification avoided?	yes	yes	yes	yes	yes	yes
7	Ref standard independent of index test?	yes	unclear	yes	yes	no	yes
8	index test described in detail to permit replication?	yes	No	yes	yes	unclear	yes
9	Reference standard described in detail to permit replication?	yes	No	yes	yes	no	yes
10	Index tests blinded?	no	Yes	yes	yes	no	unclear
11	Reference standard tests blinded?	no	No	yes	yes	yes	unclear
12	relevant clinical information? ‡	yes	Yes	unclear	unclear	yes	yes
13	Uninterpretable results reported?	yes	No	yes	yes	no	yes
14	Withdrawals explained?	yes	Yes	yes	yes	yes	yes

† Varicose veins is a chronic disease: diagnostic studies are deemed unlikely to be subject to disease progression bias - ‡ It is deemed that in clinical practice, physicians would ordinarily have clinical data available to them when interpreting a test result for varicose veins. NA=not applicable π Blomgren study not strictly a diagnostic accuracy study as compared duplex scanning with clinical examination- so some aspects of the QUADAS tool are not applicable such as the acceptable delay between tests.

Item	QUADAS tool questions	Kent et al. (1998)[139]	Rautio et al. (2002a)[140]	Rautio et al. (2002b)[141]	Salaman et al. (1995)[142]	Wills et al. (1998)[143]
1	Pts representative of normal practice?	yes	yes	yes	Yes	Yes
2	Selection criteria clearly defined?	yes	yes	yes	No	unclear
3	Acceptable ref standard?	yes	yes	yes	Yes	Yes
4	Acceptable delay between tests? †	yes	yes	yes	unclear	unclear
5	Partial verification avoided?	yes	yes	yes	yes	Yes
6	Differential verification avoided?	yes	yes	yes	Yes	Yes
7	Ref standard independent of index test?	yes	yes	yes	Yes	yes
8	index test described in detail to permit replication?	yes	yes	yes	yes	yes
9	Reference standard described in detail to permit replication?	yes	yes	yes	yes	yes
10	Index tests blinded?	Yes	yes	yes	Yes	yes
11	Reference standard tests blinded?	Yes	yes	yes	Yes	unclear
12	Relevant clinical information? ‡	Unclear	unclear	yes	yes	yes
13	Uninterpretable results reported?	Yes	yes	yes	Yes	yes
14	Withdrawals explained?	Yes	yes	yes	yes	yes

The table below shows a synthesis for the studies on HHD:

- Seven studies were judged to have a low risk of bias as they all studied patients representative of usual practice, used an acceptable reference test (duplex) and underwent this test regardless of the results of the index test;
- Two studies (Campbell et al. 2005[135] and Kambal et al. 2007[138]) were found to have a higher risk of bias particularly as they did not report the patient selection criteria clearly, describe the index and standard tests adequately or report on uninterpretable results.

Quality appraisal of HDD studies

	Campbell	Daher	Darke	Kambal	Kent	Rautio (a)	Rautio (b)	Salaman	Wills
pts representative of normal practice?									
selection criteria defined?									
acceptable ref standard?									
acceptable delay between tests?									
partial verification avoided?									
differential verification avoided?									
ref standard independent of index test?									
index test described in detail?									
ref standard described in detail?									
index tests blinded?									
ref test blinded?									
relevant clinical information?									
uninterpretable results reported?									
withdrawals explained?									

Key: yes; unclear; no

9.2.3 Data extraction table for Diagnostic studies (including hand-held Doppler)

Abbreviations

DUS	Doppler ultrasonography/duplex scan
HHD	Hand held Doppler
GSV	Great saphenous vein
LSV	long saphenous vein
MDCT	Multidetector computed tomography
NPV	Negative predictive value
PPV	Positive predictive value
SPJ	Saphenopopliteal junction
SFJ	Saphenofemoral junction
SSV	Small or Short saphenous vein

Blomgren et al 2005[47]

Setting	Sweden
Population	Patients with primary varicose veins (no previous surgery or sclerotherapy, no healed leg ulceration) referred to St Goren's Hospital between October 1997 to July 2001.
N	293 patients (343 legs)
Gender and age	217 women (256 legs)76 men (87 legs), mean age 47 (range 20 - 76)
Participation	Baseline: Pre-op duplex (156 pts/ 174 legs); no pre-op duplex (156 pts / 184 legs) 2 year follow-up: pre-op duplex (113 pts /127 legs); no pre-op duplex (106 pts / 129 legs)
Pathology	Primary varicose veins
Design	RCT
Study aims	To evaluate the effect of routine preoperative duplex imaging on the choice of surgical procedure, recurrence rate and number of reoperations 2 years after surgery for primary varicose veins
Index test	Clinical examination, + or – HHD , no preop duplex
Reference test	Pre-operative duplex
Outcomes measurement	Choice of surgical procedure, recurrence rate and number of re-operations 2 years after procedure
Results	After pre-op duplex scan, 26.5% of legs the scan suggested a different procedure from that planned. At 2 month post surgery duplex scan: 26.5% reflux in no pre-op duplex group compared with 8.8% reflux in the pre-op duplex group. At 2 years, 19 legs had reflux compared with 53 legs in the no pre-op duplex scan group.
Conclusions authors	The addition of routine preoperative duplex imaging improved the results of surgery for uncomplicated varicose veins. The numbers of residual varicose veins and reoperations during the first 2 years were reduced significantly.
Quality appraisal	Low risk of bias
Comments Abacus	Well conducted study demonstrating the importance of duplex scanning on clinical outcomes.

Campbell et al. (2005) [135]

Setting	United Kingdom (2 sites)
Population	Patients due to attend an outpatient clinics of two vascular surgical units with varicose veins and subsequently were included in a randomised trial.
n	943 patients (1218 limbs)
Gender and age	682 Women, 261 Men Median age 47.2 years, range (18-85.3)
Participation	All limbs (1218) received index and reference test
Pathology	Primary and recurrent varicose veins, but only primary varicose veins from March 2000.
Design	Prospective single blind study of consecutive patients participating in a randomised trial
Study aim	To examine the accuracy of HHD assessment in patients for whom duplex scanning would not have been requested.
Index test	HHD (by Consultants, senior surgical trainees, junior surgical trainees and by a Clinical Assistant)
Reference test	Duplex scanning (by Vascular Technologists who had access to the HHD findings).Not reported whether colour duplex
Outcomes measurement	Number of limbs examined with HHD by staff of different grades and the numbers for which duplex scans would not have been requested; Reasons for requesting duplex in practice;

	Differences observed between staff and both units in requests for duplex and in thoroughness and style of duplex reporting.
Results	In clinical practice, duplex would not ordinarily have been requested in 645 of 1052 (62%) limbs. However, among these, HHD missed significant reflux in the long saphenous vein in 18 of 645 (3%) and the small saphenous in 25 of 645 (4%). Reasons for requesting Duplex were as follows: popliteal fossa reflux (202); recurrent (94) or atypical (86) varicose veins; and possible previous thrombosis (67). Differences were observed between staff and units in requests for duplex; and in thoroughness and style of duplex reporting. Data missing for 2 limbs. Moreover HHD results of one Clinical Assistant (166 limbs) excluded given significantly poorer results.
Conclusions authors	Selective use of HHD can avoid duplex imaging for many patients, with a low failure rate for detecting correctable venous reflux. Observed variations between individuals and units in results of HHD and duplex imaging have implications for the increasing use of duplex by clinicians.
Quality appraisal	No description provided of equipment used for index and reference tests. Methods for duplex (reference standard) testing appear to differ between sites. The reference standard test was not performed blind to the HHD results, introducing review bias.
Comments Abacus	Large sample size, yet introduced much bias. Bias may arise as HHD performed by multiple individuals, so consistency of expertise in interpretation for findings elicited by HHD is not assured. It was reported that the less experienced (junior surgical trainees and clinical assistants) missed more findings than seniors with HHD; thus potential bias in the form of inter-rater reliability may exist. The duplex (reference standard) was not performed blind; HHD findings were available to the Vascular Technologists, therefore review bias is present.

Daher et al. (1997) [137]

Setting	United Kingdom
Population	Consecutive patients attending vein clinic, requiring a duplex scan of their saphenous popliteal junction (SPJ)
N	128 patients (171 limbs)
Gender and age	Female to male ratio, 3:1 Mean 54, range (18-88)
Participation	All limbs (171) received index and reference test
Pathology	Varicose veins patients with reflux at saphenous popliteal junction
Design	Prospective diagnostic comparative study
Study aims	• To determine the accuracy of hand-held Doppler assessment of patients with SPJ reflux compared with duplex scanning. • To assess the role of popliteal vein reflux in the accuracy of hand-held Doppler at the popliteal fossa.
Index test	Continuous wave hand-held Doppler assessment hand-held Doppler (CWHHD) (Huntleigh Technologies, Cardiff, U.K.) with an 8 MHz probe or a 5 MHz probe (by consultant vascular surgeon).
Reference test	duplex colour ultrasound scanning (by radiologist, blinded) Duplex scans performed using a Toshiba SSA-278A machine, with a 7.5 or 5 MHz probe.
Outcomes measurement	sensitivity, specificity, positive predictive value, negative predictive value and accuracy of continuous wave hand-held Doppler assessment compared with duplex ultrasound scanning.

Results	116 limbs showed reflux at SPJ using CWHHD; 73 of those were true positive (reflux at SPJ) using the "gold standard", DUS. 55 limbs did not have reflux at SPJ using CWHHD, with 49 of those shown to be true negative using DUS. For detecting incompetence at the SPJ, CWHHD has high sensitivity (92%) and low specificity (53%),positive predictive value (62%), negative predictive value (89%), accuracy (70%) Additionally, 17% (n=29) of all limbs had incompetence of the popliteal vein. Up to 28% (n=12) of limbs with SPJ incompetence on CWHHD and competence on DUS had incompetence of the under lying popliteal vein. If those limbs with incompetence of popliteal vein (n=12) were subtracted from those with CWHHD positive and DUS negative then the specificity would have been 61% (49/80) and the accuracy would have improved up to 82%.
Conclusions authors	CWHHD is sensitive in detecting incompetence at SPJ, though its specificity is low. The presence of SPJ incompetence on CWD should be confirmed on DUS prior to surgery.
Quality appraisal	Overall low risk of bias as clinicians were blinded and all patients underwent index and reference tests. Unclear as to duration of time delay, between appointment for initial index test and appointment for performing reference standard.
Comments Abacus	Good study, reporting accuracy of CWHHD compared with duplex. Mean delay, in days, between performing index and reference test was not reported and may be a source of bias if disease progression occurred.

Darke et al. (1997) [136]

Setting	United Kingdom
Population	Consecutive patients referred to a single vascular surgeon with primary and uncomplicated varicose veins.
n	73 patients (100 limbs)
Gender and age	55 women, 18 men Mean 47.5, range (22-74)
Participation	All limbs (100) received index and reference test
Pathology	primary and uncomplicated varicose veins
Design	Prospective diagnostic comparative study
Study aims	• To compare the findings on CWD with duplex and to evaluate the relative value and limitations of the two techniques
Index test	Continuous wave Doppler (CWD) examination was carried out by a single observer (Huntleigh dopplex 500 Probe 8 MHz).
Reference test	pulsed (Duplex) Doppler using an Acuson 128/10 colour duplex scanner with a 7MHz Linear Array probe
Outcomes measurement	Sensitivity and specificity of CWD to identifying greatsaphenous or small saphenous vein incompetence compared with duplex reference standard. Only moderate reflux (reflux time and peak velocity similar or slightly longer than the augmented and severe reflux (peak velocity and duration of reflux time equal to or exceeded augmented).
Results	87 limbs with long saphenous incompetence identified on duplex; all but 4 of which were correctly identified by CWD(4 false negatives: sensitivity 95%). There were no false positive in use of Continuous wave Doppler: (specificity was 100%.) There were 21 limbs with small saphenous incompetence on duplex, all but two of which were recognised on CWD. CWD incorrectly diagnosed reflux at the saphenopopliteal junction in five limbs (false positives) which were actually reflux in the long saphenous trunk on duplex (sensitivity 90%,

	specificity 93%.)
Conclusions authors	CWD is adequate for long saphenous incompetence. The five false positives would have resulted in inappropriate exploration of the saphenopopliteal junction, if surgery had proceeded without checking with duplex.
Quality appraisal	Duplex scan technician blind to CWD results. Unclear as to whether the single observer performing the index test was provided with patient clinical data or made clinical observations; this may have an effect on index test results.
Comments Abacus	Study objective was to compare CWD with duplex for assessing vv and to ascertain best practice for their application. CWD was found to be less accurate than duplex in the SSV. This study was found to have a low risk of bias.

Kambal et al. (2007) [138]

Setting	United Kingdom
Population	Consecutive limbs of patients undergoing saphenopopliteal junction (SPJ) surgery, who are currently subjected to two duplex scans
n	37 patients (60 limbs)
Gender and age	Not reported
Participation	All limbs (60) received the initial reference standard. Only 52 of these limbs were enrolled in the study with their index test results.
Pathology	Varicose veins receiving surgery with SPJ terminations up to 120 mm above the highest knee crease.
Design	Prospective diagnostic comparative study
Study aims	To assess whether the use of a hand-held Doppler can replace the second preoperative duplex scan.
Index test	HHD, as guided by diagnostic duplex scanning
Reference test	Duplex scanning (not reported if colour duplex)
Outcomes measurement	Distance between HHD and duplex marking of SPJ (mm), proportion of patients with 'accurate' HHD compared with duplex for SPJ localisation (<10mm distance), proportion of patients with 'inaccurate' HHD compared with duplex for SPJ localisation (>10mm distance).
Results	Eight limbs excluded from analysis as the SSV had a different anatomical termination than at the popliteal vein. The SPJ site was located by duplex scan at distances ranging between 20 mm below knee crease (BKC) and 170 mm AKC. The mode was 20 mm AKC. In 30% of the cases, the SPJ lay between 0 and 20 mm AKC. For the 52 limbs (total), 49 (94%)(95% CI 84-99%) of HHD (with duplex results guiding) accurately localised the SPJ, as compared with duplex reference standard. Three (6%) were inaccurate (>10 mm distance in marking between the two techniques) From a subgroup analysis, a higher level of accuracy was for the SPJ with reflux group, where there was found to be 100% accuracy (95% CI 87-100%) for the HHD to localise SPJ. Lesser levels of accuracy (88%) were found while using the HHD method for the SPJ no-reflux group.
Conclusions authors	HHD, guided by the routine duplex scan, can accurately mark SPJ with reflux. A second duplex is not required for marking prior to surgery. This can reduce the workload of the vascular laboratory.
Quality appraisal	The researchers in the study were made aware of the reference standard results when performing the index test, causing review bias, and potentially causing an inflated measure of diagnostic

	accuracy with HHD
Comments Abacus	Review bias may exist in study. Study concerned with accuracy of locating exact site of SPJ, as required for surgery, when using HHD compared with duplex, rather than comparing their accuracies for ascertaining the presence of reflux.

Kent et al. (1998) [139]

Setting	United Kingdom
Population	Outpatient department
N	72 patients (108 limbs)
Gender and age	52 women, 20 men Median 44.5 years, range (19-73)
Participation	All limbs (108) received index test and reference standard
Pathology	Primary, previously untreated varicose veins
Design	Prospective diagnostic comparative study
Study aims	• To determine the accuracy of hand-held Doppler assessment of patients with primary, previously untreated varicose veins compared with duplex scanning. • To assess the benefit, if any, of using tourniquet testing in these patients.
Index test	Hand-held Doppler (HHD) assessment (performed by consultant vascular surgeon) with hand-held Doppler with an 8 MHz probe (Multi-Dopplex, Huntleigh, HNE Diagnostics, Cardiff, UK). In conjunction with tourniquet
Reference test	duplex colour scanning, together with guided pulsed wave spectral Doppler (by a consultant radiologist, blinded to index test), using Siemens Q2000 machine (Siemens, Berlin, Germany), with 5 MHz curvilinear probe.
Outcomes measurement	sensitivity, specificity, positive predictive value, negative predictive value of HHD compared with duplex, proportion receiving appropriate operation planning based on test results.
Results	Sensitivity 0.93, specificity 0.91, positive predictive value 0.96, negative predictive value 0.85 for SFJ reflux. Saphenopopliteal (SPJ) reflux: Sensitivity 0.82, specificity 0.85, positive predictive value 0.43, negative predictive value 0.96. Additionally, results are provided for great saphenous vein, mid-thigh perforator, popliteal vein and superficial femoral vein reflux. Appropriate surgical procedure based on HHD results was selected on 75 limbs (70%). Unnecessarily extensive surgery would have been performed on 25 limbs (23%) and inadequate surgery performed on seven limbs (7%) based on HHD alone. Surgical planning results: If a policy of duplex scan requesting on limbs with (i) suspected SPJ reflux (n = 33), (ii) no identifiable site of reflux (n = 8), or (iii) suspected posterior thigh perforator reflux (n =1) on HHD had been used, duplex scanning would be required in only 39% of limbs assessed. With this implemented, an appropriate surgical procedure would be performed in 101 (94%) limbs, that unnecessary saphenofemoral junction ligation would be performed in 5 (5%) limbs and that inadequate surgery would be performed in only 1 (1%) limb.
Conclusions authors	HHD is a reliable test when compared with duplex scanning in assessing SFJ and LSV reflux. Assessment of SPJ reflux using HHD is not good, with a low positive predictive value, although the high negative predictive value suggests that absence of SPJ reflux is accurately assessed. Addition of tourniquet testing to HHD assessment is inaccurate and

	unhelpful in the assessment of deep venous reflux and mid-thigh perforator reflux. The referral of only patients with suspected SPJ reflux, posterior thigh reflux or no detectable source of reflux for duplex would reduce the workload of the vascular laboratory without compromise of patient care quality.
Quality appraisal	Unclear as to whether the single observer performing the index test was provided with patient clinical data or made clinical observations; this may have an effect on index test results.
Comments Abacus	Well reported study with a low risk of bias with extensive accuracy data for reflux at six limb sites, as assessed by HHD and duplex, including surgical implications.

Lee et al. (2008)[48]

Setting	Korea
Population	Consecutive patients referred to department of radiology for varicose vein evaluation over 3 month period.
n	100 patients (151 limbs with vv)
Gender and age	55 women, 45 men Mean age 54.9, range (18-84)
Participation	All patients (n=100)(151 limbs) underwent 3D-CT (index test). Of these, 50 patients (61 limbs) underwent DUS (reference standard)
Pathology	All patients had visible varicose veins. Varicosity ranked severe in 17 limbs, moderate in 63, mild in 68. No varicosities in the other 51 limbs. CEAP NR
Design	Comparative diagnostic study
Study aims	• To evaluate the imaging quality of CT venography for clinical evaluation of superficial venous system • To compare CT and duplex findings about varicose veins
Index test	MDCT venography. CT examinations were performed using an 8-MDCT (LightSpeed Ultra) or 16-MDCT (Sensation 16) with patient in supine position. Two experienced radiologists performed the 3D reconstruction
Reference test	Duplex (Doppler) sonography performed by one radiologist using a colour Doppler sonograph (Accuvix XG) and a 7.5-MHz linear probe. Patients in a 10-20 degree from vertical semierect position.
Outcomes measurement	Assessment of overall quality of 3D volume-rendered images- 2 radiologists evaluated the quality of images using a 3 level grading system (excellent, fair or poor). Prediction of Great Saph Vein insufficiency by CT.
Results	Using duplex sonography as reference standard: - prediction of Great Saph Vein insufficiency with CT venography had a sensitivity of 98.2% (56 of 57 cases) and a specificity of 83.3% (14 of 17 cases). - 15 insufficient small saphenous veins: sensitivity 53.3% (8 out of 15) and specificity 94.9% (56 out of 59)
Conclusions authors	CT venography has disadvantages over duplex; patients had to lie on specially constructed buttock and heal pads to prevent superficial compression of the vein and the need for contrast medium and ionizing radiation. Advantages: three-dimensional images yields comprehensive anatomic information
Quality appraisal	Partial verification bias may be present as the sample selected for to receive the reference standard (50 of 100) patients was not reported as random. Possible review bias as is unclear as to

	whether surgeons requesting duplex sonography were blinded to results of 3D-CT
Comments Abacus	Study focus was to correlate CT and duplex findings about varicose veins. CT has disadvantages over duplex in that it requires catheterisation and injection of contrast medium and associated radiation dose.

Rautio et al. (2002a)[140]

Setting	Finland
Population	Patients with varicose veins who were referred to a department of surgery for surgical treatment of varicose veins
n	111 patients (142 limbs)
Gender and age	96 women, 15 men Mean 42, range (23-76)
Participation	All limbs (142) received index test and reference standard
Pathology	Primary, uncomplicated varicose veins
Design	Prospective diagnostic comparative study
Study aims	• To compare the clinical and HHD evaluation of primary varicose veins with duplex scanning
Index test	clinical and HHD examination (by consultant general surgeon) using 8MHz probe (Hadeco mini-doppler ES-100X, Hayashi Denko CO. Ltd, Arima, Japan).
Reference test	Duplex colour scanning (by consultant vascular radiologist, blinded) with a 7.5MHz probe and venous flow settings (Toshiba Power Vision 8000, Japan)
Outcomes measurement	Sensitivity, Specificity, Positive predictive value, Negative predictive value, Kappa coefficient to detect reflux at sites of SFJ (n=142), LSV(n=142), SPJ (n=112). An audible flow signal lasting longer than one second was used as the threshold for significant reflux. Operation planned for patients on the basis of HHD findings, operation planned on the basis of duplex findings.
Results	<table><tr><th></th><th>SFJ</th><th>LSV upper thigh</th><th>LSV lower thigh</th><th>LSV calf</th><th>SPJ</th></tr><tr><td>Sensitivity%</td><td>56</td><td>58</td><td>62</td><td>67</td><td>23</td></tr><tr><td>Specificity%</td><td>97</td><td>84</td><td>82</td><td>81</td><td>96</td></tr><tr><td>PPV%</td><td>98</td><td>87</td><td>84</td><td>77</td><td>43</td></tr><tr><td>NPV%</td><td>44</td><td>51</td><td>58</td><td>72</td><td>91</td></tr><tr><td>Kappa coefficient for reflux</td><td>38</td><td>36</td><td>41</td><td>48</td><td>24</td></tr></table> Overall, the treatment plan based on HHD examination was changed after duplex scanning in 13 limbs (9%). Clinical examination failed to correctly plan the treatment in 21 (26%)of 80 proposed operations.
Conclusions authors	HHD preoperative vein evaluation in primary, uncomplicated varicose veins is unsatisfactory. Duplex ultrasonography should be considered as the preoperative diagnostic method of choice. The results strengthen the case for duplex ultrasound to be performed preoperatively in all patients with primary uncomplicated varicose veins.
Quality appraisal	Well reported study with low risk of bias.
Comments Abacus	Study objective was to evaluate HHD accuracy in planning operations. Study had well defined eligibility criteria and provides insight into how a duplex scan modified the varicose

	veins treatment pathway in patients initially evaluated with HHD. Accuracy of HHD can be dependent upon the site of reflux i.e. SPJ less accurate than SFJ.

Rautio et al. (2002b)[141]

Setting	Finland
Population	Consecutive patients scheduled for surgical treatment of varicose veins who were referred to a department of surgery
n	49 patients (62 limbs)
Gender and age	44 women, 5 men Median 45.5, range (19-66)
Participation	All limbs (62) received index test and reference standard
Pathology	primary, previously untreated, uncomplicated varicose veins
Design	Prospective diagnostic comparative study
Study aim	• To assess the effect of clinical and HHD examinations compared with duplex ultrasonography on the planning of the operative procedure for varicose veins
Index test	Examined clinically and then with HHD (by a general surgeon) with 8 MHz probe (Hadeco minidoppler ES-100X, Hayashi Denko, Arima, Japan)
Reference test	duplex colour scanning (by a 'blinded' vascular radiologist) with a 5 MHz probe (Toshiba Power Vision 8000, Japan)
Outcomes measurement	Sensitivity, Specificity, Positive predictive value, Negative predictive value, Kappa coefficient to detect reflux at sites of SFJ and 3 LSV sites. Operation planned for patients on the basis of HHD findings, operation planned on the basis of duplex findings.
Results	<table><tr><td></td><td>SFJ</td><td>LSV upper thigh</td><td>LSV lower thigh</td><td>LSV calf</td></tr><tr><td>Sensitivity%</td><td>64</td><td>49</td><td>54</td><td>47</td></tr><tr><td>Specificity%</td><td>93</td><td>92</td><td>86</td><td>90</td></tr><tr><td>PPV%</td><td>97</td><td>96</td><td>88</td><td>83</td></tr><tr><td>NPV%</td><td>45</td><td>32</td><td>47</td><td>61</td></tr><tr><td>accuracy</td><td>71</td><td>58</td><td>65</td><td>68</td></tr></table> The overall accuracy of HHD compared with duplex scanning was 0.71. The treatment plan was changed after duplex scanning in 6 limbs (10%).
Conclusions authors	Most operations on primary varicose veins can be performed on the basis of clinical and HHD examinations by an experienced surgeon. Duplex ultrasonography can be used selectively in the patients with suspected saphenopopliteal junction (SPJ) reflux or equivocal HHD findings. In most clinical situations (90%), duplex scanning provides no crucial advantage over a clinical examination with supplementary HHD.
Quality appraisal	Well conducted study with low risk of bias.
Comments Abacus	Study objective was to evaluate HHD accuracy in planning operations. Study had well defined eligibility criteria. Provides detailed insight into how a duplex scan modified the varicose veins diagnostic and treatment pathway in patients initially evaluated with HHD. Authors reported weakness of study was the lack of comparative data on the SSV system (reported in Rautio 2002a).

Salaman et al. (1995)[142]

Setting	United Kingdom
Population	Patients awaiting varicose vein surgery or attending a vascular outpatient clinic with symptomatic varicose veins.
n	42 patients (72 limbs)
Gender and age	Not reported
Participation	All limbs (72) received index and reference test
Pathology	Symptomatic varicose veins. Presenting symptoms were: unsightly varicosities (56%), skin pigmentation (25%) and painful or aching legs (19%). Previous varicose vein surgery had been performed in 18% of patients.
Design	Prospective diagnostic comparative study
Study aim	To assess the sensitivity and specificity of HHD compared to colour duplex imaging in patients presenting with symptomatic varicose veins.
Index test	HHD, performed with a Dopplex® MD2 (Huntleigh Nesbit. Evans Ltd, Cardiff, UK) bi-directional handheld Doppler unit using an 8 MHz probe. Patient data recorded computer using Dopplex® Reporter for Windows V2.0 software (© Huntleigh Technology plc1993), with use of rubber tourniquet
Reference test	Colourduplex ultrasonography using a Toshiba SPA270A scanner with a 5 MHz. linear array probe.
Outcomes measurement	sensitivity, specificity, positive predictive value, accuracy of HHD compared with Duplex.
Results	SFJ: PPV 98%, sensitivity 92%, specificity 94% SPJ: PPV 63%, sensitivity 56%, specificity 89% Accuracy data for perforators also reported.
Conclusions authors	HHD assessment of the SFJ is sensitive and specific. Assessment of other sites can be erroneous; due to anomalies between the great and small saphenous connections with pelvic veins. With HHD, long saphenous tributaries can mask, or be mistaken for SPJ incompetence. HHD assessment of varicose veins prior to surgery is useful. Care is needed on interpretation of findings, particularly in the popliteal fossa. HHD diagnosis of incompetence in deep or perforator veins should be followed by further evaluation with colour duplex ultrasound scanning or venography.
Quality appraisal	Overall low risk of bias. Unclear as to duration of time delay, between appointment for initial index test and appointment for performing reference standard. Patients excluded from enrolment were not stated, if any.
Comments Abacus	Well reported study with sensitivity, specificity and PPV data for reflux at six limb sites, as assessed by HHD and duplex. The reported results are similar to other studies; unreliability of diagnosis of deep vein incompetence with HHD alone and reduced accuracy due to anatomical variability of long saphenous vein tributaries at the sapheno-popliteal junction. Study demonstrates that with HHD, a high proportion of subjects with positive test results for incompetence are being correctly diagnosed (reflected by 98% PPV).

Wills et al. (1998)[143]

Setting	Australia
Population	Patients referred to a sole specialist vascular surgeon during a 1-year period, for whom medical records were available.
N	188 patients (315 limbs)
Gender and age	142 women, 46 men Mean 54.1, range (21-79)
Participation	All limbs included (315) had previously received index test and reference standard
Pathology	Primary and secondary (5.1% limbs) varicose veins
Design	Retrospective study
Study aims	To evaluate the role of duplex scanning, in addition to clinical and Doppler assessment
Index test	Clinical assessment and HHD evaluation: Parks hand-held 8 MHz Doppler probe (Parks Medical Electronics, Shaw, Aloha, OR, USA)
Reference test	Duplex scan, using a Toshiba 270 scanner (Toshiba Corp., Otawarashi,Tochigi, Japan) with a 5 MHz probe and colour flow imaging (performed by vascular technician)
Outcomes measurement	Sensitivity, specificity and accuracy at (SFJ, SPJ, perforators, deep veins) for HHD versus duplex. Analysis of the clinical significance of errors in recognizing sites of reflux.
Results	Sensitivity for HHD (%): 71.2 (SFJ), 36.1 (SPJ), 43.6 (Perforators), 29.2 (deep veins). Specificity (%): 70.9 (SFJ), 92.1(SPJ), 78.7(Perforators), 94.8 (deep veins). Only 40.3% of legs had a completely accurate clinical and Doppler assessment when compared with the duplex results. 121 limbs (of the original 315) on clinical and HHD evaluation were identified to have primary saphenofemoral incompetence alone. Under the assumption that appropriate surgery had been performed on these, 28.9% may well have had significant improvement, but unrecognized sites of reflux were likely to remain untreated at surgery, and therefore result in recurrent varicose veins.
Conclusions authors	Conclusions: Clinical and HHD assessment is unreliable. Routine duplex scanning is likely to reduce recurrence by identifying sites of reflux with greater accuracy. The HHD ability to evaluate incompetence of perforators is poor, adding little to clinical examination. HHD Saphenopopliteal junction evaluation is also poor, with an accuracy of only 64%.
Quality appraisal	Data derived from past medical records; Unreported as to duration of time delay before the reference standard was subsequently performed. Potential for disease progression bias. Unclear whether clinician performing diagnostic tests were blinded.
Comments Abacus	Study limited by retrospective design and unclear whether blinding took place or the amount of time elapsed between HHD and duplex. Study population included 38.7% recurrent varicose veins.

9.2.4 Overview of included diagnostic studies for hand-held Doppler

Nine studies compared duplex ultrasound with hand-held Doppler.

9.2.4.1 Patients

The patient population across the studies was predominantly primary, uncomplicated varicose veins.

Only three out of ten studies reported the CEAP classification of their patients. The CEAP classification illustrates a mild severity of the disease in most cases:

- Rautio et al. (2002b)[141]:all 62 limbs were CEAP 2 or 3;
- In a second study by the same author: 126 out of 137 limbs were CEAP 2 or 3[140];
- Kent and Weston (1998)[139] had only 10% of patients with a CEAP classification greater than three.

Patient numbers ranged between 37 and 188, with the exception of one larger study with 943 patients from the Campbell et al trial[135]. The conclusions of four studies are based on tests performed on 100 or less limbs [48 136 138-143].

9.2.4.2 Outcomes

Of the ten studies, seven studies [48 136 139-143] reported on both diagnostic accuracy (location and extent of reflux) and clinically relevant outcomes (treatment plan or unnecessary treatment).

One study[137] reported on diagnostic accuracy only (location and extent of reflux).

The two last studies did not report on diagnostic accuracy outcomes [135 138].

- Kambal et al. 2007[138] focused on the preoperative marking of the saphenopopliteal junction (SPJ) prior to surgery by comparing the accuracy of HHD with duplex. The outcome in this study was the distance in millimetres between the SPJ site located by HHD and the SPJ site located by duplex, with distances greater than ten millimetres deemed not acceptable for surgical accuracy.
- Campbell et al. 2005[135] reported on whether clinicians had requested a duplex scan and the extent of missed reflux by HHD.

9.2.4.3 Diagnostic accuracy of hand-held Doppler versus Duplex ultrasound

Diagnostic accuracy at the saphenofemoral junction

Diagnostic accuracy (location and extent of reflux) of the saphenofemoral junction (SFJ) was reported in six of the nine HHD vs duplex studies [136 139-143]. Overall, the sensitivity and specificity of HHD compared with duplex in the assessment of reflux in the great saphenous vein (GSV) was high.

In four studies with patient populations largely consisting of patients with primary, uncomplicated varicoses, the sensitivity ranged from 95% to 71.2% [136 139 142 143]. Lower sensitivity was reported in the studies conducted by Rautio et al. (2002a and 2002b) 64% to 56%[140 141]

Specificity was between 100% and 91% except in the study from Wills et al (70.9%) [136 139-143].

The likelihood ratio value indicates the value of the test for increasing certainty about a positive diagnosis[144]. The likelihood ratio of a positive test ranged from 95 in the Darke study[136] to 2.44 in the Wills study[143]. These results show a high probability of a true positive reflecting the sensitivity results reported above. Correspondingly, the likelihood ratio of a negative test ranged from low values of 0.05 and 0.07 in the Darke[136] and Kent studies[139] to higher values 0.40 and 0.45 in the Rautio[112] and Wills[143] studies.

Diagnostic accuracy at the saphenopopliteal junction

Diagnostic accuracy in the small saphenous vein (SSV) was assessed in six studies [136 137 139 140 142 143]. The sensitivity and specificity of HHD at the saphenopopliteal junction (SPJ) were lower than at the SFJ. A prospective study by Daher et al. (2001) compared the diagnostic accuracy of HHD with duplex specifically at the SPJ. One hundred and seventy-one limbs were evaluated: 116 limbs showed reflux at SPJ using HHD, however only 73 of these were true positives on duplex, reporting a sensitivity of 92% and a specificity of 53% (PPV=62%, NPV+89%, accuracy = 70%) at the SPJ[137]. The likelihood ratio of a positive test in this study was calculated to be 1.96 which shows the likelihood of a patient being accurately diagnosed with SPJ incompetence is approximately twice that of a negative result. This was the lowest likelihood ratio positive calculated for the SPJ studies and is a reflection of the lower specificity reported in this study.

In a smaller study, Darke et al. (2001) compared the diagnostic accuracy of continuous wave doppler with duplex in 21 limbs with SSV incompetence. They reported a sensitivity of 90% and a specificity of 93%[136]. The likelihood ratio positive was also high (12.85) and the likelihood ratio negative low (0.1).

A lower accuracy was detected by Kent and Weston (1998) who reported a sensitivity of 82% and sensitivity of 80% at the SPJ in primary varicose veins (108 limbs)[139], although the likelihood ratio of a positive test was calculated to be 4.1 indicating the likelihood of a patient having SPJ incompetence is approximately four times that of a negative result.

However, lower rates of accuracy were detected in the other three studies that reported SPJ findings. The sensitivity ranged from 56% in the Salaman et al. (1995)[142] study to 36.1% in Wills et al. (1998)[143] and 23% in the Rautio et al. (2002a)[140] study. Specificity was greater than 80% in all studies except Daher et al. (2001) which reported a lower specificity of 53%[137]. The calculated likelihood ratio positive values in these three studies ranged from 4.6 to 5.75 and the likelihood ratio negative values between 0.49 to 0.8 [140 142 143].

Overall, the ranges reported for diagnostic accuracy at the saphenopopliteal junction were large: sensitivity reported in six studies ranged from 92% to 23% and the specificity from 96% to 53% [136 137 139 140 142 143].

9.2.4.4 Summary: diagnostic accuracy of hand-held Doppler

The table below summarises the results from the eight studies evaluating the accuracy of HHD at the SFJ and SPJ.

Summary of sensitivity and specificity results from hand-held Doppler versus duplex

Study	Study population	Sensitivity SFJ	Specificity SFJ	Sensitivity SPJ	Specificity SPJ
Campbell et al. 2005[135]	Primary and recurrent, majority primary; CEAP NR	NR	NR	NR	NR
Daher et al. 2001 [137]	Patients requiring SPJ scan CEAP: NR	NR	NR	92% LRP=1.96	53% LRN=0.1
Darke et al. 1997 [136]	Primary and uncomplicated CEAP: NR	95% LRP=95	100% LRN=0.05	90% LRP=12.85	93% LRN=0.1
Kambal 2007 [138]	Patients with clinically suspected SPJ reflux CEAP: NR	NR	NR	NR	NR
Kent and Weston 1998 [139]	Primary uncomplicated varicose veins; CEAP 1 : 0.9% CEAP 2: 89% CEAP 4: 8.3% CEAP 6: 1.8%	93% LRP=10.3	91% LRN=0.07	82% LRP=4.1	80% LRN=0.2
Rautio 2002a [140]	Primary varicose veins CEAP 1 : 4% CEAP 2: 47% CEAP 3: 42% CEAP 4: 8%	56% LRP=18.6	97% LRN=0.45	23% LRP=5.75	96% LRN=0.8
Rautio 2002b [141]	Primary uncomplicated varicose veins CEAP: all 2 or 3	64% LRP=9.14	93% LRN=0.38	NR	NR
Salaman 1995 [142]	Primary uncomplicated varicose veins 82%, secondary 18% CEAP:NR	92% LRP=15.3	94% LRN=0.08	56% LRP=5.1	89% LRN=0.49
Wills 1998 [143]	Primary uncomplicated varicose veins 95%, secondary 5% CEAP:NR	71.2% LRP=2.44	70.9% LRN=0.40	36.1% LRP=4.6	92.1% LRN=0.69

LRP= Likelihood ratio positive; LRN=likelihood ratio negative
T – These studies did not report on diagnostic accuracy outcomes

Diagnostic accuracy of hand-held Doppler

- **Overall, the sensitivity and specificity of hand-held Doppler compared with duplex ultrasound in the assessment of reflux in the great saphenous vein was found to be high;**
- **The accuracy of hand-held Doppler in the small saphenous vein, particularly the popliteal fossa, was found to be less reliable as was the assessment for anatomical deformities.**

9.2.5 Clinical Consequences of the findings: hand-held Doppler versus Colour duplex ultrasound

Seven studies [135 136 138-141 143] reported on the clinical consequences of their diagnostic findings and particularly on how the diagnosis based on HHD findings would have impacted on the surgical plan or influenced unnecessary treatment.

9.2.5.1 Hand held doppler versus Duplex ultrasound for preoperative assessment

Darke et al.[136] compared duplex scanning and continuous wave Doppler in the assessment of uncomplicated varicose veins. The Doppler:

- correctly identified 83 out of 87 limbs with long saphenous incompetence, with four false negatives ;
- correctly identified 19 out of 21 limbs in the assessment of the small saphenous system. Moreover five false positives in the SSV would have lead to inappropriate exploration of the SPJ without duplex ultrasound[136].

Rautio et al. (2002a) concluded that duplex rather than HHD should be considered as the preoperative diagnosis method of choice[140]. They found that the treatment plan based on HHD examination was changed after duplex scanning in 13 out of 142 limbs (9%). If surgery had gone ahead only based on HHD it would have led:

- to the stripping of the wrong saphenous vein for 2 limbs;
- to stab avulsion only for 7 limbs whereas duplex plan was LSV/SSV stripping operation ;
- to a wrong treatment for four legs: HHD planned LSV stripping and duplex scanning led to another decision as stab avulsion only140.

In another study Rautio et al. (2002b) concluded that in most clinical situations duplex scanning provides no advantage over HHD because in 56 (out of 62 limbs) duplex did not affect the surgical treatment. They proposed to use duplex if the clinician suspected reflux at the saphenopopliteal junction. A weakness of this study was that the authors only investigated the SFJ[141].

Kent and Weston (1998) reported similar findings to those from the above studies, with appropriate surgical procedure being carried out in 94% of108 limbs based on HHD findings[139]. However, unnecessary saphenofemoral junction ligation would be performed in 5 limbs and inadequate surgery would be performed in 1 limb.

Wills et al (1998)[143] concluded that the treatment of patients based on HHD and clinical and Doppler assessment resulted in 29% of site of reflux that would be left untreated.

A prospective study by Campbell et al.(2005) examined the accuracy of HHD assessment in patients for whom duplex scanning would not have been requested. The clinicians concluded that a duplex scan would not have been requested in 645 of the 1052 limbs (62%). In the group of patients labelled as “unnecessary duplex“ (2/3 of the patients) 7% had undiagnosed reflux: reflux of LSV was missed in 3% (18 of 645 limbs) and reflux in the SSV was missed in 4% (25 of 645 cases)[135]. There is bias in this study that excluded the poor results from one clinician (166 limbs examined) who missed 32% of LSV reflux. This observation highlights the importance of expertise in the use of HHD.

9.2.5.2 Hand-held Doppler to replace a second Duplex ultrasound before surgery

A study by Kambal et al. (2007) assessed whether the use of HHD can accurately locate the position of the SPJ site before surgery in patients who have had an initial diagnostic duplex scan[138]. In patients with SPJ reflux, HHD was 100% accurate in localising the site compared to an accuracy of 88% (22 out of 25 patients) in patients with no SPJ reflux. The authors conclude that HHD used after an initial duplex scan can accurately mark a refluxing SPJ prior to surgery[138].

9.2.5.3 Summary: clinical significance of hand-held Doppler versus Colour Duplex ultrasound

Surgical plans remained unchanged for 90% of the patients when a Colour Duplex ultrasound was performed after a hand-held Doppler. However the accuracy of HHD to determine the surgical treatment was higher in the great saphenous vein than in the assessment of the popliteal fossa.

9.3 QUALITY APPRAISAL FOR INCLUDED SYSTEMATIC REVIEWS

	Internal validity					Overall assessment					
Study	**Appropriate and clearly focussed question?**	**Is a description of the methodology described?**	**Literature searches adequate?†**	**Study quality assessed and taken into account?‡**	**Was pooling of data appropriate? (If applicable)**	**Bias minimisation? (++, + or -)**	**If biased, how would bias affect results?**	**Types of study included**	**Research questions answered?**	**High quality systematic review?**	**comments**
Adi et al., 2004 [67]	Well covered	Well covered	Adequately addressed	Well covered	Not applicable	+		RCTs, case series	Partly	yes	Older RCTs
Alberta Medical Advisory 2004 [63]	Well covered	Well covered	Adequately addressed	Adequately addressed	Not applicable	++		SR,RCTs	Yes	yes	Good report but older data reported
ASERNIP 2008 [58]	Well covered	Well covered	Well covered	Well covered	Not applicable	++		SR, RCTs and nRCTs	Yes	yes	Same data as Leopardi review
Brar et al., 2010 [56]	Adequately addressed	Adequately addressed	Adequately addressed	Not addressed	Not addressed	++		RCTs	Yes	yes	
CADTH 2010 [65]	Well covered	Adequately addressed	Poorly addressed	Not reported	Not applicable	++		HTA report, systematic reviews, RCT and controlled clinical trials, cost-effectiveness studies	Yes	yes	Limited literature search, only 1 RCT and this evidence is covered in Ontario HTA (2010).
Chevallier et al., 2005 [50]	Adequately addressed	Poorly addressed	Adequately addressed	Poorly addressed	Not applicable	-	Results could favour either intervention if studies with high risk of bias were included	All study types	unclear	no	Weak methodology
Coleridge Smith et al., 2009 [53]	Poorly addressed	Poorly addressed	Adequately addressed	Not addressed	Not applicable	-	Results could favour either intervention if studieswith high risk of bias were included	RCTs, case-series	Unclear	no	Weak methodology
Dutch guideline[52]	Adequately addressed	poorly addressed	Adequately addressed	poorly addressed	Not applicable	-	Results could favour either	SRs, RCTs, NRCTs,	Yes	no	Weak methodology

	Internal validity					Overall assessment					
Study	**Appropriate and clearly focussed question?**	**Is a description of the methodology described?**	**Literature searches adequate?†**	**Study quality assessed and taken into account?‡**	**Was pooling of data appropriate? (If applicable)**	**Bias minimisation? (++, + or -)**	**If biased, how would bias affect results?**	**Types of study included**	**Research questions answered?**	**High quality systematic review?**	**comments**
							intervention if studies with a high risk were included	non-comparative trials, opinions			
Hamel-Desmos et al., 2009 [60]	Adequately addressed	Adequately addressed	Adequately addressed	Not addressed	Adequately addressed	++		RCTs	yes	yes	
HAS 2008a [66]	Well covered	Adequately addressed	Adequately addressed	Adequately addressed	Not applicable	++		Reviews, comparative studies, non-comparative studies.	yes	yes	
HAS 2008b [69]	Well covered	Adequately addressed	Adequately addressed	Adequately addressed	Not applicable	++		Reviews, comparative studies, non-comparative studies.	yes	yes	
IQWIG 2009 [55]	Well covered	Well covered	Adequately addressed	Poorly addressed	Not applicable	-	Results could affect either intervention if studies with a high risk of bias were included	Guidelines, SR	partly	yes	Not included because not useful
Jia et al., 2007 [35]	Adequately addressed	Well covered	Well covered	Adequately addressed	Adequately addressed	++		RCTs, non-RCTs, case series, case reports, conference abstracts	yes	yes	Limited long-term RCTs
Leopardi et al., 2009 [57]	Well covered	Well covered	Well covered	Well covered	Not applicable	++		SR, RCTs and nRCTs	Yes	yes	
Luebke et al. 2008a [36]	Adequately addressed	Adequately addressed	Poorly addressed	Poorly addressed	Not applicable	-	Heterogeneity of studies seriously threatens the validity of the SR and meta-	RCTs, CCTs	no	yes	Different study types and different study populations have been combined in meta-analysis Not included because research questions not

	Internal validity					Overall assessment					
Study	**Appropriate and clearly focussed question?**	**Is a description of the methodology described?**	**Literature searches adequate?†**	**Study quality assessed and taken into account?‡**	**Was pooling of data appropriate? (If applicable)**	**Bias minimisation? (++, + or -)**	**If biased, how would bias affect results?**	**Types of study included**	**Research questions answered?**	**High quality systematic review?**	**comments**
							analyses				answered
Leubke et al., 2008b [32]	Adequately addressed	Adequately addressed	well covered	Adequately addressed	Poorly addressed	-	Heterogeneity affects results of analyses	RCTs, n-RCTs, retrospective	no	yes	meta-analysis includes a mix of case-series and RCTs- heterogeneity limits conclusions of meta-analysis
Luebke et al. 2008c, [68]	Well covered	Well covered	Well covered	Poorly addressed	Poorly addressed	+	Validity of results limited by methodology	RCTs, case series and retrospective and case reports	no	yes	meta-analysis includes a mix of case-series and RCTs- heterogeneity limits conclusions of meta-analysis
Martinez et al., 2005 [37]	Well covered	Well covered	Well covered	Adequately addressed	Not applicable	++		RCTs	yes	yes	patient populations not well defined, only 4 studies used CEAP classification
MSAC 2008 [33]	Well covered	Well covered	Well covered	Well covered	Not applicable	++		SR, RCTs and nRCTs	yes	yes	Valid report. References covered by Ontario HTA (2010)
NICE 2004 [6]	poorly addressed	poorly addressed	poorly addressed	poorly addressed	Not applicable	-	Limited search would limit results	Case series	no	no	Rapid non-comprehensive review
NICE 2003 [34]	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Not applicable	+		RCTs, case series	partly	yes	only 1 RCT included with small patient numbers and not blinded
NICE 2009 [61]	Adequately addressed	Adequately addressed	Adequately addressed	Not addressed	Not applicable	+		RCTs, case series, case reports and UK clinical audit	yes	yes	Rapid review lacking robust methodology
Nicolaides et al., 2008 [7]	Adequately addressed	poorly addressed	Not addressed	Not addressed	Not applicable	+		SRs, RCTs, NRCTs, non-comparative trials	yes	no	limited details on methodology or searches
Ontario 2010 [64]	Well covered	Well covered	Well covered	Well covered	Not applicable	++		systematic evidence	yes	yes	good quality report, with most up to date RCTs,

	Internal validity					Overall assessment					
Study	**Appropriate and clearly focussed question?**	**Is a description of the methodology described?**	**Literature searches adequate?†**	**Study quality assessed and taken into account?‡**	**Was pooling of data appropriate? (If applicable)**	**Bias minimisation? (++, + or -)**	**If biased, how would bias affect results?**	**Types of study included**	**Research questions answered?**	**High quality systematic review?**	**comments**
								(Syst) reviews, RCT, non-RCTs, surveillance, case series			Has additional RCTs Disselhoff 2008 and Theivacumar 2009 not covered in Rees 2009
Palfreyman et al., 2009 [70]	Well covered	Well covered	Well covered	Adequately addressed	Not applicable	++		RCTs	yes	yes	Included RCTs were poor methodologically, often no randomisation reported
Rees et al., 2009 [29]	Well covered	Well covered	Well covered	Adequately addressed	Not applicable	++		SR, RCTs and nRCTs	yes	yes	Valid report. Good range of references covering EVLT, RFA and sclerotherapy.
Rigby et al., 2004 [30]	Well covered	Well covered	Well covered	Well covered	Not applicable	++		RCTs	yes	yes	The evidence from this review has been updated in more recent SRs.
Tisi et al., 2007 [49]	Well covered	Adequately addressed	Poorly addressed	Not addressed	Not applicable	-		RCTs	yes	no	No search terms reported brief methodol.
Tisi et al., 2006 [62]	Well covered	Well covered	Well covered	well covered	Not applicable	++		RCTs	yes	yes	
Van des Bos et al., 2009 [59]	Adequately addressed	Adequately addressed	Adequately addressed	Poorly addressed	Poorly addressed	+		RCTs, case series and retrospective	No	yes	meta-analysis includes a mix of case-series and RCTs- heterogeneity limits conclusions of meta-analysis
Van den Bos 2009b[54]	Adequately addressed	poorly addressed	poorly addressed	Not addressed		+		All study types	yes	no	Safety data from Van Den Bos 2009a
Van Neer et al., 2003 [51]	Poorly addressed	Poorly addressed	Adequately addressed	Poorly addressed	Not applicable	-	Results could affect either intervention if studies with a high risk of bias were included	All study types	unclear	no	Weak methodology

† adequate=Medline, Embase, Cochrane and hand searching from 1990 onwards

‡ adequate=A well conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. There must be an indication of such an assessment.

9.4 DATA EXTRACTION TABLE FOR INCLUDED SYSTEMATIC REVIEWS

9.4.1 Reviews evaluating multiple treatments

Reference	High quality study?	Inclusion criteria		Summary of Results					
		Treatments included	**General patient inclusion criteria**	**Number and type of studies included**	**Sclerotherapy**	**Surgery**	**EVLT**	**RFA**	**Summary**
Brar et al., 2010 [56]	yes	laser and RFA therapies compared with open surgery (great saphenous vein)	varicose veins of the great saphenous vein	Nine RCTs		The incidence of wound infection is significantly higher with open surgery compared to EVLT.	Pooled data demonstrate that return to work is significantly faster than open surgery. The 2-year occlusion rate for the VNUS device is comparable to that of open surgery.	RFA has marginally higher recanalisation rates than EVLT, but the heterogeneous nature of this data make this treatment difficult to compare to EVLT and surgery	Endovascular treatment of VVs (Great saphenous vein) is safe, and efficacy at 3 months is at least equivalent to that of open surgery. .
Leopardi et al, 2009 [57] and ASERNIP 2008 [58]	yes	Multiple interventions. varicose vein treatments including conservative therapy, sclerotherapy, phlebectomy, ELT, RFA and surgery	patients having treatments for varicose veins of the legs, both superficial and complicated	17 (4 SR, 10 RCTs and 3 non-RCTs)	Sclerotherapy showed superior clinical and cosmetic results compared with surgery in the short term (<12 months) which declined rapidly from this point, confirming that surgery was more durable and showed superior treatment outcomes	Surgery (ligation without stripping) appeared more effective than phlebectomy in regard to combined treatment failures and in the occurrence of new veins.	One SR with no direct comparison between ELT and surgery; Comparable results with both techniques but no definite CCL possible (lack of direct comparisons, mostly short term - 12 weeks- and similar outcomes of interest in RCTs = QOL, return to work) Evidence from one SR but difficult interpretation	One SR (2004) comparing surgery with RFA found no significant difference in reflux-free status of patients following RFA and surgery (stripping with or without ligation). RFA was found to be at least as safe as surgery however results on the effectiveness of RFA with some studies reporting it to be as clinically effective as surgery but one study showing it to be inferior to	Overall much of the RCT and nonrandomized comparative evidence was of poor quality, making judgements on safety and efficacy outcomes between the treatments difficult. Serious adverse events were uncommon in both groups and generally occurred in <2% of the patient or limb.

Reference	High quality study?	Inclusion criteria		Summary of Results					
		Treatments included	General patient inclusion criteria	Number and type of studies included	Sclerotherapy	Surgery	EVLT	RFA	Summary
								surgery.	
Luebke 2008 [36]	Yes	RFA, EVLT and foam sclerotherapy	Patients over 18 years with clinically documented primary venous reflux, confirmed by duplex ultrasonography of the great or small saphenous veins.	radiofrequency obliteration (RFA)(32studies) , endovenous laser therapy (EVLT)(32), foam sclerotherapy(22 studies). Results are based on meta-analyses combining different study types.	Foam sclerotherapy of varicose veins was associated with a higher recurrence rate in patients with saphenofemoral incompetence compared to the rates after EVLT or RFA treatment. Compared to surgery (2 studies)no significant difference was found and there was substantial heterogeneity between studies.	NR	EVLT had the best results concerning the long-term effectiveness para-meters for "occlusion at the end of follow-up" and "recanalization, recurrence or development of new veins", compared to RFO and FS.; follow-up time variable (29 studies in meta-analysis)	RFA associated with the worst efficacy results compared to EVLT and FS regarding "complete occlusion at the end of follow-up". When ORs between the different meta-analyses were compared, variable follow-up.	The SR mixed all kinds of study design with uncertainties about their quality appraisal. The ground for the meta analyses raise serious questions.
Rees et al., 2009 (NHS) [29]	Yes	Minimally invasive techniques (RFA, EVLT, sclerotherapy) compared with surgery	adults >15 years with VV or great saphenous vein incompetence or CVI or venous ulcers	18 in total:sclerotherapy (5 RCTs) - EVLA (4 RCTs and 2 CCTs) -- Laser (5 RCTs)	EVLA resulted in fewer complications than surgery. Both surgery and EVLT had similar post-treatment pain scores.		EVLA has largely similar long term recurrence rates and better immediate outcomes (earlier return to work and less pain) when compared with surgery.		Although EVLA and RFA are both effective in the short term, there is a lack of evidence for long term results. There is the potential to improve both patient comfort and recovery rates with the endovascular procedures.

Reference	High quality study?	Inclusion criteria		Summary of Results					
		Treatments included	General patient inclusion criteria	Number and type of studies included	Sclerotherapy	Surgery	EVLT	RFA	Summary
Van den Bos et al., 2009 [59]	yes	minimally invasive therapies (EVLT, RFA, sclerotherapy) compared with surgical ligation and stripping		64 studies in total: stripping (13), UGFS (30), EVLA (30) and RFA (19) but 9 RCts only	**Sclerotherapy vs conservative therapy** One RCT reported significantly more patients with an improvement in the anatomical extent of their veins following sclerotherapy at 1 year follow-up (p<0.05).. At 2 year follow-up, **there was no difference in QOL and** 76.9% of responders had developed new varicosities, with no sig difference between the treatment groups. **Sclerotherapy vs phlebectomy.**One RCT, reporting on the treatment of lateral accessory veins found phlebectomy patients to have lower recurrence rates than sclerotherapy patients at 1 and 2 year follow-up. Another RCT found recurrence at 10 year follow-up to be significantly higher following phlebectomy.	**Sclerotherapy vs surgery** two RCTs found sclerotherapy to be significantly better than surgery (ligation with stripping) at 1 year follow up. This effectiveness declined at 2 year follow-up, there was no difference between sclerotherapy and surgery. An RCT that compared sclerotherapy with ligation without stripping found surgery to be subjectively and objectively better than sclerotherapy at 3 year follow-up (p<0.05)	Of the three minimally invasive techniques, EVLA was superior to foam sclerotherapy *(P* = .013) and RFA (P;0,016) . No significant difference between Foam and RFA (P=0,27).		Lack of RCTs to support the conclusions. Meta-analysis carried out using all different study types so difficult to interpret results.

9.4.2 Reviews evaluating EVLT

Reference	High quality study?	Number of studies included	Inclusion	Summary of Results
CADHT 2009 [65]	Yes	11 studies in total: types included:HTA (1), SR (4), RCT (1), CCT (1), cost-effectiveness (2), costing studies (2)	studies comparing EVLT with other treatments for the management of varicose veins were included	The majority of studies for EVLT were relatively short-term and there is a lack of robust, sufficiently powered RCT evidence to make comparisons to other minimally invasive techniques. There is some evidence that the short-term clinical effectiveness of EVLT is similar to surgery with fewer adverse events however long-term data is missing.
HAS 2008[66]	Yes	33 studies; 2 studies vs crossectomy-vein removal; 2 studies comparing different laser procedure parameters, 1 study vs crossectomy and stripping, 13 prospective case series, 9 retrosective studies, 6 studies on perfecting the procedure.	Saphenous vein occlusion by laser For comparative trials: randomisation, results presented separately for the treatment arms, patients followed with echography.	Laser occlusion of the femoral part of the great saphenous vein is a therapeutic option; its efficacy at 1 year has been shown. The efficacy-safety ratio of laser occlusion of the femoral part of the great saphenous vein has been demonstrated at 1 year. The data for small saphenous vein occlusion by laser is currently insufficient. Preliminary data are encouraging, but safety remains to be established.
MSAC 2008[33]	Yes	effectiveness (5 total): 5 controlled clinical trials (2 RCTs); safety (35 total): 5 comparative, 35 case series	patients with documented primary venous reflux of the great or small sapheous veins, in whom sclerotherapy is likely	The evidence shows that EVLT is an effective treatment for occluding the saphenous vein, and is at least as effective as the conventional surgical operation. EVLT patients reported fewer symptoms of varicose veins and better scores on a number of quality of life domains than ligation and stripping patients; however, many of these differences were statistically significant for only a short period of time after treatment. EVLT patients were also reported to require less time to return to work than

Reference	High quality study?	Number of studies included	Inclusion	Summary of Results
				patients who had undergone ligation and stripping, and mean operating time for EVLT was found to be significantly shorter than for conventional surgery.
Ontario 2010 [64]	Yes	59 studies in total: HTA (3); SR (11); 29 cohort, 4 cost studies, 12 RCT.	EVLT for VV (great or small saphenous veins). Review also compared EVLT with surgery (main comparator) and the minor comparators: foam sclerotherapy and RFA.	EVLT was found to be as effective as surgery as assessed by imaging of the treated veins, symptomatic relief for the patient and QoL outcomes. Recurrence rates were similar apart from neovascularisation which was significantly higher with surgery. Patient outcomes were positive for EVLT; the use of local anaesthesia makes a faster recovery period. EVLT had lower rates of minor complications than open surgery.

9.4.3 EVLT RCTs from the review of Rees et al., 2009 [29]

Study	Follow-up	Total No. of patients	Inclusion criteria	Methods	Results
Darwood et al., 2008 [107]	1, 6, 12 weeks and 1 year after treatment	103	Patients with SFJ and GSV reflux	Surgery vs EVLT (by stepwise laser withdrawal) vs EVLT (by continuous laser withdrawal)	GSV incompetency abolished in 41/42 legs in EVLT (1); 26/29 EVLT (2) and 28/32 surgery (p=0.227) Median return to normal activity was 2 days EVLT vs 7 days for surgery(p=0.001) Patient satisfaction similar in both intervention groups.
De Madeiros et al., 2006[108]	Clinical review at 7, 30 and 60 days and duplex ultrasound after 30 days	20	Symptomatic varicose veins on both lower limbs, bilateral insufficiency of the entire GSV on duplex scanning	Twenty patients with bilateral GSV incompetence underwent bilateral random comparison of EVLT of GSV and SSV on one side compared with surgery (SFA ligation and GSV and SSV stripping).	Post-operative pain between legs was similar. More oedema and bruising reported in limbs treated by surgery compared to EVLT. 70% of patients preferred the laser side (p=0,018)
Kalteis et al., 2008 [106]	Colour duplex ultrasound at	100	Patients with GSV incompetence	100 patients randomised to either surgery (SFJ ligation and stripping) or	Occlusion rate for both methods at 4 and 16 weeks No difference between post-op pain or QoL between

Study	Follow-up	Total No. of patients	Inclusion criteria	Methods	Results
	1, 4 and 16 weeks			EVLT and SFJ ligation.	groups Return to work sooner for surgery than EVLT (14 days vs 20days,p=0.054)
Rasmussen et al., 2007 [109]	6 months	121	Varicose veins of CEAP class C2 – C4 with aetiology: primary, anatomy: superficial and pathophysiology: reflux, age 18- 80 years, GSV incompetence defined by reflux time > 0.5sec by ultrasound imaging	EVLT of GSV (69 legs) vs SFV ligation and LVA stripping (68 legs). Both used phlebectomy on superficial varicose veins	Procedure failure similar Six month efficacy data similar between groups Higher post-operative pain after surgery Mean time to return to normal activities or work same between groups

9.4.4 Reviews evaluating RFA

Reference	High quality study?	Number of studies included	Inclusion criteria	results	summary
Adi et al., 2004 [67]	Yes	2 RCTs and 17 case series	patients with complicated varicose veins	Compared with both stripping alone and stripping plus ligation, RFA was associated with a reduction in post-operative pain relief at 2-weeks and no significant difference in adverse events	Further studies providing unbiased estimates of the relative long-term effects of RFA in comparison to conventional surgical approaches for varicose veins are needed.
Luebke et al., 2008c [68]	Yes	6 RCTs	patients over the age of 18 years with clinically documented primary venous reflux confirmed by duplex ultrasonography of the great or small saphenous veins; the patients were suitable for either of the	There were significant reductions in tenderness and ecchymosis at 1 week and significantly fewer hematomas at 72hrs, 1 week and 3 weeks associated with RFA.	QoL results significantly favouring RFA over surgery included return to normal activity and return to work.

Reference	High quality study?	Number of studies included	Inclusion criteria	results	summary
			treatment options.		
NICE 2003[34]	Yes	1 RCT, 13 case series	Patients eligible for RFA	RFA reported excellent occlusion rates in fifteen patients. Better pain scores and a faster return to work were recorded in the RFA group compared with the stripping group.	Results of this review are based on one RCT with a high risk of bias.
HAS 2008b [69]	yes	18 studies	RFA	RFA was found to be superior with regards to quality of life at 1 week (1 of 5 studies).Relapse rate appears to be similar (RFA vs crossectomy-stripping).	

9.4.5 RFA RCTs from Rees et al., 2009 [29]

Study	Follow-up	Total No. of patients	Methods	Results
Hinchcliffe et al., 2006[110]	1, 6, and 12 weeks and 1 year	16	16 patients with recurrent bilateral GSV incompetence. 32 legs randomised to RFA and phlebectomy or redo surgery stripping and phlebectomy.	Shorter procedure time than surgery. Decreased pain and less bruising for RFA Ultrasound showed no GSV continuity after RFA but partial occlusion in 3 legs.
Lurie et al., 2003 (EVOLVeS trial) [111]	3 days, 1, 3 and 16 weeks	80 (legs not patients)	RFA with below knee phlebectomy (44 legs) compared with surgery (SFA ligation and GSV stripping) and below knee phlebectomy (36 legs)	Shorter procedure time for RFA. Immediate treatment success rate was 95% RFA vs 100% surgery Faster return to work RFA (mean 4.7 days) vs surgery (12.4 days) ($p<0.05$) Less bruising and haematoma in RFA QoL favoured RFA at 3 days and 1 week, similar to surgery at 4 months post-procedure
Lurie at al., 2005 EVOLVeS trial follow-up[114]	1 year and 2 years	1 year (45 pts), 2 years (65 pts)	As above	Cumulative recurrence rates for varicose veins were 14% for RFA and 21% for surgery ($p>0.05$) Better QoL score for RFA re-appeared at 1 and 2 years. Lower pain for RFA ($p<0.05$)

Study	Follow-up	Total No. of patients	Methods	Results
Rautio et al., 2002 [112]	1, 4 and 7 weeks	28	RFA and phlebectomy (15 patients) versus surgery (SFJ ligation and stripping with phlebectomy) (13 patients)	Longer procedure time for RFA compared with surgery (75 mins vs 57 mins, p=0.003) Pain scores significantly less in RFA group (p<0.05) No reflux detected (by duplex) in RFA patients. Same number of complications (minor) between groups Quicker return to work and restoration of physical function in the RFA group (6.5 vs 15.6 days, p<0.001)
Stotter et al., 2006 [113]	Day 1, week 1, 2 and 6, and 1 year	40	RFA (n=20) vs surgery (n=20) SFJ ligation and stripping and cryostripping (n=20). No phlebectomies were performed.	Longer mean treatment time for RFA vs surgery RFA less haematoma, QoL and pain scores and return to normal activity all in favour of RFA at 6 weeks (p<0.05) RFA patients were more satisfied with the operation (p<0.001) At 1 year, no clinical difference between RFA and surgery.

9.4.6 Reviews evaluating sclerotherapy

Reference	High quality study?	Number of studies included	Inclusion criteria	Summary of Results
Alberta HTA 2004 [63]	Yes	1 SR, 1 evidence review and 5 RCTs	all sclerotherapy techniques (with or without ultrasound guidance; using liquid or foam sclerosing agents). Comparators: conservative measures (such as compression therapy), other non-surgical options (such as laser therapy), surgical procedures, no treatment.	There is no strong evidence to support or not support the use of sclerotherapy for symptomatic varicose veins. Standard sclerotherapy appears to be efficacious in the management of reticular varicosities and telangiectasia. The agents polidocanol, sodium tetradecyl sulfate, and hypertonic saline are potentially safe and effective sclerosants in the short-term, but there is no standard protocol for their use. The place of sclerotherapy as the first line of treatment for large varicose veins (saphenous or non-saphenous) remains controversial; however following surgery, sclerotherapy may achieve good results for varicose veins that have not fully disappeared or recur.

Reference	High quality study?	Number of studies included	Inclusion criteria	Summary of Results
Hamel-Desnos 2009 [60]	Yes	8 - 6 (RCT's) for saphenous veins, 2 comparative trials for reticular veins and telangiectases	primary varicose veins- divided into 2 groups - saphenous veins and reticular veins and telangiectases, this distinction may be crucial for conclusion	efficacy results from a meta-analysis, greatly favour foam over liquid sclerotherapy : foam 76.8% (95% CI 71-82) versus liquid 39.5% (95% CI 33-46); p<0.0001 Side-effects were rare for all the trials, with one trial reporting no side effects. Foam shows much greater efficacy compared to liquid. There was no statistically significant differences in side effects between foam and liquid sclerotherapy.
Jia 2007 [35]	Yes	Sixty-nine studies(eight RCTs, one registry study, three non-randomized comparative study, 27 case series and five case reports, 24 conference abstracts. One study was unpublished	varicose veins (great and/or small saphenous vein incompetence) or varicosities in adults aged 16 years and over .	There is insufficient evidence to allow a reliable comparison of its effectiveness with that of other minimally invasive therapies or surgery. High-quality RCTs with a follow-up period of at least 3 years are required to determine its proper place in clinical practice. Furthermore, we must distinguish treatment of saphenous veins and treatment of reticular veins or telangiectases.
NICE 2009[61]	Yes	10 (2 RCTs, 4 case series, 4 case reports),	patients with varicose veins	Long term data on recurrence rates from RCTs show that this procedure has better efficacy outcomes than surgery however as this is still a relatively new procedure longer term follow up is required.
Tisi 2006 [62]	Yes	17 RCTs	Sclerotherapy versus other treatment options: a) Sclerotherapy versus graduated compression stockings for varicose veins with superficial venous incompetence. b) Sclerotherapy versus graduated compression	Evidence from RCTs suggests that the choice of sclerosant, dose, formulation (foam versus liquid), local pressure dressing, degree and length of compression have no significant effect on the efficacy of sclerotherapy for varicose veins. The

Reference	High quality study?	Number of studies included	Inclusion criteria	Summary of Results
			stockings or observation for varicose veins in the absence of superficial venous incompetence. c) Sclerotherapy versus laser treatment or no treatment (i.e. simple follow-up) in people with thread veins. 2. Comparison of different sclerosants 3. Comparison of injection techniques, bandaging and compression techniques and repeat treatment intervals.	evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins following surgery and thread veins.

9.4.7 Sclerotherapy RCTs from Rees et al., 2009 [29]

Study	Follow-up	Total No. of patients	Methods	Results
Belcaro et al. 2000 [115]	10 years	121	Ultrasound-guided LSC (polidocanol) of GSV (n=32) compared with surgery to SFJ alone or surgery combined with sclerotherapy (n=33)	Sapheno-femoral incompetence at 10 years was 19% for sclerotherapy alone and 0% for the other treatment options. Distal venous incompetence was 44% for sclerotherapy, 36% for surgery alone and 16% for combined surgery and sclerotherapy.
Belcaro et al., 2003 [116]	10 years	887	887 patients with VV and SV incompetence were randomised to 6 different treatment options (LSC (n=123); high-dose LSC (n=112), closed loop ligation (n=132), stab avulsion (n=122), E-FSC (n=129), surgical ligation then LSC (n=131).	Decrease in venous reflux was generally comparable across all groups. Overall 51% of patients had new varicose veins at 10 years compared with 44% at 5 years. Low dose LSC is less effective than FSC and high dose LSC.
Bountouroglou et al., 2006 [118]	3 weeks and 3 months	58	Ligation of SFJ and stripping (n=28)vs FSC of GSV and ligation of SFJ (n=30)	Mean treatment time was 45 mins for foam and 85 mins for surgery. Mean return to work was 2 days (0-6 days) for foam and 8 days (5-20 days) for surgery ($p<0.001$).. Short term GSV closure rate was lower for foam

Study	Follow-up	Total No. of patients	Methods	Results
				(87%) than surgery (93%). AVVQ score similar between groups at 3 months (p<0.001).
Michaels et al., 2006 (REACTIV trial) [11]	2 years	1009	RCT divided patients into minor, moderate and severe VV of LSV with reflux. Group 1 (34 patients): minor VV conservative treatment vs LSC Group 2 (77 patients): LSC vs surgery Group 3 (246 patients) conservative treatment vs surgery. Remaining 652 patients were observed for disease progression.	Surgery and LSC showed significant clinical improvement and QoL scores SFJ ligation, GSV stripping and multiple phlebectomies is clinically more effective than conservative treatment. Only group 3 (surgery group) was large enough to show clear results. Early complications of sclerotherapy included blistering and ulceration (7.1% of patients), phlebitis (15.4%) and pigmentation of skin (7.7% of patients)
Wright et al., 2006 [119]	Duplex ultrasound at 1 and 4 weeks, 3 months and some patients 1 year.	710	Patients with GSV VV randomised into 3 groups: Surgery (n=94) vs LSC (n=125) vs varisolve (n=437).	Complete occlusion in 67% FSC patients and 86% surgery patients. Surgery had higher occlusion rates than varisolve at 3 (87% vs 68%) and 12 months (86% vs 63%) Standard sclerotherapy had similar occlusion rates to varisolve at 3 months (88% vs 93%) but lower occlusion rate at 12 months (76% vs 89%) (p<0.001) 6 reports of neurological symptoms after varisolve all resolving in 24 hours. Deep vein thromboses occurred in 11 varisolve and 1 sclerotherapy patient (after this dose of varisolve was reduced from 60ml to 30 ml).

LSC=liquid sclerotherapy; FSC= foam sclerotherapy; varisolve= foam

9.4.8 Reviews focused on surgery evaluation,

Study	High quality study?	Number of studies included	Inclusion	Summary of Results	Comments
Rigby et al., 2004 [30]	Yes	9 RCTs	Surgery vs sclerotherapy	Three RCTs showed that sclerotherapy was more effective in the first year, but this outcome diminished so that by five years, surgery was the most effective intervention.	RCT evidence has been updated in more recent systematic reviews

9.4.9 Reviews evaluating hosiery

Study	High quality study?	Number of studies included	Inclusion	Summary of Results	Comments
Palfreyman et al., 2009 [70]	yes	25 (1 SR, 9 RCTs, 12 n-RCTs, 2 guidelines)	Patients with uncomplicated varicose veins	The effect of compression stockings on the symptoms of varicose veins was equivocal, although some studies did report an improvement in leg symptoms; there were limitations of assessment of subjective symptoms.	Methodological quality of included RCTs was poor. Patient populations were variable. Randomisation and blinding often not reported.

9.4.10 Reviews evaluating drugs

Study	High quality study?	Number of studies included	Inclusion	Summary of Results	Comments
Martinez et al., 2005 [37]	Yes	59 RCTs	1) Natural products (a) flavonoids: rutoside, french maritime pine bark extract, grape seed extract, diosmine and hidrosmine, disodium flavodate; (b) saponosides: centella asiatica. (2) Synthetic products: calcium dobesilate, naftazone, aminaftone and chromocarbe.	There is not enough evidence to globally support the efficacy of phlebotonics for chronic venous insufficiency. There is a suggestion of some efficacy of phlebotonics on oedema but this is of uncertain clinical relevance.	RCTs evaluated oral phlebtonics in CVI study population. Results are not separated into the different stages of CVI and only 4 of the included studies used CEAP to classify the disease.

9.5 QUALITY APPRAISAL FOR INCLUDED PRIMARY STUDIES

9.5.1 Quality appraisal tool

The SIGN RCT quality appraisal tool was used by the research team to assess the risk of bias of the study. The legend below explains the quality markers and the grading system agreed by the research team.

Item	Well covered	Adequately addressed	Poorly addressed
Research question	Question clear and well explained	Question clear	Research aim not clearly stated
Randomisation	Method of randomisation robust such as computer generated from a remote site	Randomisation method adequate	Poor randomisation methodology such as alternate patients
Allocation concealment	methods of concealment clearly described with strong likelihood of concealment in both investigators and participants being maintained	methods of blinding not clearly described but study described as single/double blinded	concealment of investigators and participants described but it is likely from the description reported that participants or investigators enrolling participants could possibly foresee treatment assignments
Patient group comparable	Study authors report that baseline demographics between studies were similar (with or without having performed statistical analyses), or on inspection of baseline demographics, the reviewer can see no differences between the groups that are likely to subject results to bias.	Patient demographics in each treatment arm not reported by authors as being similar, but reviewer perceives there to be little risk of bias due to any observed differences between groups studied. If patient groups are dissimilar for a demographic variable likely to cause bias, appropriate	reviewers perceives there to be differences between groups in demographics, which have not been adjusted for in analyses.
Dropouts and intervals described?	Number of withdrawals for each arm and reasons for withdrawal clearly described. Additionally, the point of withdrawal for each of those withdrawing during the study cycle is clearly described	Withdrawal numbers are described for each arm, and reasons, but no description of point of withdrawal during follow up or treatment period.	Study does not describe number or reasons for withdrawal by treatment arm; but for all patients enrolled in study as a whole.
Analyses conducted in ITT population?	If data is missing, missing data is clearly shown in results to have been imputed using appropriate methods to perform statistical analyses, using the intention to treat set or full analysis set for treatment arms.	Methods describe use of intention to treat principles, but the results do not clearly state 'n' for the treatment groups or there is evidence to show that ITT has not been performed.	'As-treated' analysis has been performed

Not addressed (i.e. not mentioned, or indicates that this aspect of study design was
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

9.5.2 Quality appraisal of treatment RCTs: results

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
Almeida 2009[78]	Adequately addressed	Adequately addressed	Poorly addressed	Poorly addressed	Adequately addressed	Not reported	Poorly addressed	Single blinded study, does not bias patient-reported outcomes, but can bias investigator outcomes; not mentioned in how many patients the limbs were per group; American and European sites may have differences in surgery methods	Either treatment arm could be affected	yes	Low
Assandian 2008 [72]	Poorly addressed	Poorly addressed	Not addressed	Not addressed	Poorly addressed	Adequately addressed	Yes	No details of randomisation method, no allocation concealment or blinding, little information of baseline demographics	Results may favour the investigated treatment as no blinding. This was a pilot study only.	Yes	High
Blaise 2010[79]	Well covered	Well covered	Well covered	Well covered	Adequately addressed	Adequately addressed	No	Good protocol with allocation concealment and three years of double blinding. No reasons for dropouts given and no	Low chances of bias	Yes	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
								comment on comparability of base line demographics but they appeared similar.			
Carradice 2009[80]	Adequately addressed	Poorly addressed	Not addressed	Adequately addressed	Adequately addressed	Adequately addressed	No	No detail of randomization process although sealed envelopes used for allocation concealment. No blinding.	Results may favour the experimental treatment if that were favoured by the investigating team	Yes	Low
Carradice 2011 [71]	Adequately addressed	Adequately addressed	Not addressed	Adequately addressed	Adequately addressed	Adequately addressed	yes	Well designed study but limited by no blinding.	No blinding could influence investigators	Yes	Low
Carandina 2008 [97]	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Not addressed	Adequately addressed	No	Good randomization process and allocation concealment. No data for baseline demographics. No intervals for drop-outs given.	Data could be biased if baseline demographics were not comparable, but no information given	Yes	Low
Christenson 2010 [81]	Adequately addressed	Adequately addressed	Poorly addressed	Not addressed	Adequately addressed	Adequately addressed	No	Pre and post op evaluations done by operating surgeon although DUS performed by independent observer (not	There may be some bias toward the treatment favoured by the surgeon as there was no blinding	Yes	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
								stated as blinded). No allocation concealment.			
Disselhoff 2008a[82]	Adequately addressed	Adequately addressed	Not addressed	Adequately addressed	Adequately addressed	Well covered	No	Acknowledges lack of blinding but aimed to minimise bias by using 1 surgeon with no preferences for either treatment and using patient reported outcomes such as AVVSS and VCSS	Low risk of bias	Yes	Low
Disselhoff 2008b[83]	Adequately addressed	Poorly addressed	Not addressed	Adequately addressed	Adequately addressed	Adequately addressed	Modified ITT	No description of randomization process, no blinding. Baseline demographics given but no comment as to their comparability, drop outs shown but no intervals	Results may favour the experimental treatment if that were favoured by the investigating team	Yes	Low
Doganci 2010[84]	Well covered	Adequately addressed	Not addressed	Not addressed	Adequately addressed	Adequately addressed	Yes	No blinding.	Results may favour the experimental treatment if that were favoured by the	Yes	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
									investigating team		
Figueiredo 2009[85]	Adequately addressed	Adequately addressed	Not addressed	Poorly addressed	Adequately addressed	Poorly addressed	Not known	No blinding. No drop out intervals described. Different success/failure markers for each treatment.	Results may favour the experimental treatment if that were favoured by the investigating team	Yes	Low
Gale 2010 [73]	Poorly addressed	Poorly addressed	Not addressed	Adequately addressed	Adequately addressed	Not addressed	Unknown	No details of randomization process given. No mention of blinding or of drop-outs/loss to follow up. Some differences in baseline demographics.	There may be some bias toward the treatment favoured by the surgeon as there was no blinding.	Yes	High
Goode 2010[88]	Adequately addressed	Adequately addressed	Adequately addressed	Not addressed	Adequately addressed	Poorly addressed	No	Efforts made to blind patients and assessors	Low risk of bias	Yes	Low
Hamel-Desnos 2010[74]	Adequately addressed	Adequately addressed	Poorly addressed	Not addressed	Poorly addressed	Not addressed	Yes	Some independent observers used but no blinding. Baseline demographics had significantly older patients in one arm (p=0.0178). No drop outs described but short study (28 days).	Results may favour treatment as although assessors were independent they were not blinded, older patients in one arm may be detrimental to that	Yes	High

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
									outcome		
Hamel-Desnos 2008[87]	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Poorly addressed	Not reported	Patients and assessors were blind to the treatment. Incomplete outcome data was not addressed. It is unclear whether the analysis was performed on the ITT population.	Minimal bias	Yes	Low
Helmy ElKaffas 2011[99]	Poorly addressed	Adequately addressed	Not addressed	Not addressed	Adequately addressed	Adequately addressed	No	No blinding. Author notes significantly older patients in the surgical group, (P=0.02).	Results may favour the RFA group due to increased age in the surgical group	Yes	Low
Houtermans-Auckel 2009[86]	Adequately addressed	Adequately addressed	Poorly addressed	Adequately addressed	Adequately addressed	Well covered	Not addressed	"Due to practical issues, patients and investigators were not blinded". In one group, 6/52 (11%) dropped out, in the other group, 2/52 (4%) dropped out.	Intervention group (with the stockings) may be in favour	Yes	Low
Klem 2009[100]	Poorly addressed	Adequately addressed	Not reported	Adequately addressed	Adequately addressed	Well covered	Adequately addressed	Blinding not possible, due to intervention type; QoL baseline scores	Either treatment arm could be affected	yes	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
								not comparable; 19 and 30 patients lost in follow-up; some patients changed intervention after randomisation			
Martinez-Zapata 2008[89]	Adequately addressed	Adequately addressed	Not addressed	Not addressed	Adequately addressed	Adequately addressed	Yes	Double blind placebo controlled trial but no details in text of how observer blinding was accomplished.	Low risk of bias	Yes	Low
Maurins 2009[75]	Well covered	Poorly addressed	Not addressed	Not addressed	Poorly addressed	Adequately addressed	Yes(no drop - outs)	No details of randomization method. No mention of blinding, experienced phlebologists carried out pre and post –op assessments but not blinded. Only baseline figures for CEAP given.	Risk of bias through lack of blinding. Cannot confirm baseline demographics were similar	Yes	High
Menyhei 2008[91]	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Adequately addressed	Well covered	Adequately addressed	Well conducted and reported study	Low risk of bias	yes	Low
Ouvry 2008[90]	Adequately addressed	Poorly addressed	Not reported	Not reported	Adequately addressed	Adequately addressed	Not addressed	Follow-up was relatively short	Either treatment arm could be affected	poorly	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
Pares 2010[98]	Adequately addressed	Adequately addressed	Poorly addressed	Not addressed	Poorly addressed	Well covered	Yes	No details of allocation concealment or blinding; Base line demographics had larger proportion of females in 1 arm (80.2% vs. 65.9% in the other arms)	Results may favour treatment as although assessors were independent they were not blinded, author states 1 out of the 3 interventions could be identified by the scars	Yes	Low
Pronk 2010[96]	Poorly addressed	Adequately addressed	Not addressed	Not addressed	Adequately addressed	Adequately addressed	Yes	No blinding in methodology therefore risk of bias	Results could favour either treatment	No clear question posed	Low
Rabe 2008[92]	Poorly addressed	Poorly addressed	Not reported	Not reported	Adequately addressed	Well covered	Poorly addressed	No blinding of clinicians or patients. No blinding of outcome assessor at 3 month follow up.	Either treatment arm could be affected	yes	Low
Rasmussen 2010 [93]	Adequately addressed	Adequately addressed†	Not addressed	Adequately addressed	Adequately addressed	Poorly addressed	No	No Detail of randomisation process. Possible bias due to no blinding of surgeon or research nurse at recall assessments. All patients considered	Results may favour either treatment offered as assessment carried out by the operating surgeons.	Yes	Low

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
								failures were removed from the study.			
Shepherd 2010[94]	Poorly addressed	Adequately addressed	Poorly addressed	Adequately addressed	Adequately addressed	Well covered	Adequately addressed	Assessors not blinded for "practical reasons" although primary outcomes were patient reported and patients were blinded	Either treatment arm could be affected	yes	Low
Subramonia 2010[95]	Adequately addressed	Adequately addressed	Poorly addressed	Not reported	Adequately addressed	Well covered	Adequately addressed	Blinding impossible due to intervention type	Either treatment arm could be affected	partially	Low
Theivacumar 2008[76]	Adequately addressed	Poorly addressed	Not addressed	Not addressed	Adequately addressed	Not addressed	Yes	No details of randomisation method, no allocation concealment or blinding, No comment as to comparability of baseline demographics and there are anomalies? Drop -outs not mentioned but it was a short study (12 weeks)	Results may favour the investigated treatment as no blinding. Inconsistencies in length of vein treated and age in baseline demographic may adversely affect results in those groups.	Yes	High
Yamaki 2009[77]	Adequately addressed	Poorly addressed	Not reported	Not reported	Adequately addressed	Not reported	Poorly addressed	No blinding mentioned; drop outs not reported and	Either treatment arm could be affected	partially	High

		Internal validity						Overall assessment			
Study	**Appropriate and clearly focussed question?**	**Randomised?**	**Outcome blinded?**	**Allocation concealment?**	**Patient group comparable?**	**Dropouts and intervals described?**	**Analyses conducted in ITT population?**	**Bias minimisation?**	**If biased, how would bias affect results?**	**Research question answered?**	**Risk of bias**
								method of analysis was subjective rather than quantitative			

9.6 DATA EXTRACTION TABLES OF INCLUDED RCTS

9.6.1 Included RCTs evaluating EVLT

Reference	Details of intervention/ anaesthetic used	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/ adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Carradice 2011 [71] UK 1 site Hospital setting	EVLT Tumescent LA	Conventional surgery GA	280 EVLT n=140, Surgery n=140	Primary symptomatic, unilateral varicose veins (GSV). Isolated SFJ incompetence and GSV reflux (reflux of 1 sec) on DUS. Perigenicular vein diameter >4mm	Generic QoL using UK SF-36, EuroQoL 5D, AVVQ	EVLT: local tumescent anaesthesia, GSV cannulated percutaneously with the patient in reverse Trendelenburg. A 5-Fr catheter was introduced into the vein using the Seldinger technique, and its tip positioned at the SFJ under US guidance. 600nm laser fibre was introduced via the catheter for laser ablation of the GSV, endovenous laser energy was delivered using an 810nm diode laser generator set at 14W. Surgery: all surgical procedures were performed under GA. Flush SFJ ligation was followed by ligation of all tributaries back to the second branch, and inversion stripping of the GSV to the knee.	1 week, 6 weeks, 3 months and 1 year	EVLT took longer mean 67 mins vs 61 mins; p=0.002). The surgery group took longer to return to normal activities (median 14 vs 3 days;p<0.001).	Complications were relatively rare in both groups, but sensory disturbance, (surgery n=13 vs EVLT n=4, p=0.02) haematoma (surgery n=11 vs EVLT n=1, p=0.003) and infection (surgery n=8 vs EVLT n=2, p=0.048)rates were significantly higher after surgery. EVLA patients reported less pain than surgery from day 1 (p=0.004 to <0.001).	SF-36: after 1 week, surgical group deteriorated in 5 of the 8 domains; EVLT caused significant deterioration in only 2 domains (p<0.001). After initial deterioration, both groups resulted in sig overall improvements in 5 out of 8 domains. From 4 weeks, there were no differences between the groups. AVVQ scores:Both groups had the same AVVQ scores after 1 week (p<0.001) (worsening). There were no significant differences in AVVQ scores between the groups at any time point.	This RCT showed both surgery and EVLT to be effective treatments with the less invasive technique EVLT resulting in postoperative improvements in QoL and less pain.
Christenson 2010 [81]	EVLT 980 nm GA or spinal	High ligation and surgical	EVLT N= 104 limbs (4 failures exclude	Progressive superficial venous insufficiency (Widmer class 0 to	Abolition of the GSV or presence of reflux on	Ligation of the SFJ and of all tributary veins was performed through a 1- to 2-cm groin incision. A standard stripper was inserted in the GSV, and	DUS at 6 hours and12 days. 1 and 2 years	No significant difference between the groups regarding treatment	Small accidental skin burn in 1 EVLA patient. No major	Similar times for the return to normal activity and scores for	Useful study for direct comparison of EVLA with

Reference	Details of intervention/ anaesthetic used	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/ adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Switzerland 1 site Hospital setting	anaesthesia, 90% ambulatory	stripping (HL/S)	from the analysis); Surgery N=100 limbs	III) and/or C2-6, S, Ep, As2-3 ±As1 and Ap17-18, Pr, according to the CEAP. Pre-treatment DUS scanning demonstrated reflux at the saphenofemoral confluence during Valsalva manoeuvre together with a GSV diameter of 5 to 15 mm at 3 cm from the saphenofemoral junction with the patient prone and truncal reflux >0.5 seconds	DUS; treatment time; treatment related complications; SF-36; AVVSS; VVCSS	the vein was stripped top down either to just below the knee or at the ankle (4-mm skin incision). EVLT ablation was performed using a 980-nm diode laser under DUS guidance		time (31.4 ± 7.8 minutes [HL/S] and 32.0 ± 7.4 minutes [EVLT], respectively). All GSV's absent or abolished 6 hours post-treatment DUS (both groups). Two GSVs in the EVLT group reopened and three partially reopened at 1 year. No open GSVs occurred in HL/S limbs. At 2 years two more GSVs in the EVLT group were partially reopened.	complications after treatment were recorded. HL/S limbs had significantly more postoperative hematomas(12 limbs vs 5 limbs; p=0.076) than EVLT limbs, and EVLT patients reported more bruising (15 limbs EVLT vs 2 limbs surgery; p<0.002).	postoperative pain were reported. VCSS, AVVSS, and Short Form-36 scores did not reveal any group differences.	surgery and 2 year follow up. Similar efficacy found between the treatments but more side effects with EVLA, 4/104 failures excluded, some reopeness at 2 years. No reason given why 221 limbs failed inclusion for randomisation.Improved blinding of outcome would have increased the study's usefulness.
Disselhoff 2008 [82] The Netherlands 1 site Hospital setting	EVA without SFJ ligation GA or local	EVA with SFJ ligation GA or local	No ligation of SFJ N= 43 limbs; Ligation of SFJ N= 43 limbs	Patients with primary, symptomatic, bilateral varicose veins. CEAP C2 venous disease. SFJ incompetence and GSV reflux from the groin to below the knee, 20-75 years	Operative time. Complications; wound closure (MHCS); mean pain, mean reduction in physical activity; mean duration of sick leave. Recurrence (DUS)	Heparin on day of surgery for all patients. The GSV, 5 cm below the knee, was accessed under US guidance and the tip of the laser positioned 0.5-1 cm below the SFJ. 12-Watt intermittent or 14-Watt continuous laser energy was delivered at a pullback rate of 0.2 cm/s. High ligation was performed through a 4-cm-long incision in the groin, with flush division of the GSV and division of all tributaries behind the second level of division.	2 years	Two-year life table analysis showed freedom from recurrence in 83% of 43 limbs (95% CI; 67-95%) in the EVA without ligation group and in 87% of 43 limbs (95%; CI 73-97) of limbs in the EVA with ligation group (P=0.47). Thirty-eight (88%) treated GSV segments were ablated completely in the EVA without ligation group and 42	There were no significant differences between the groups concerning bruising (54% in the EVA group and 58% in the EVA with ligation group, N.S.), pain score (3.6 S.D. 2.1 and 3.6 S.D. 2.4, N.S.), tightness along the course of the GSV(84% and 79%, N.S.), and	VCSS scores improved significantly in both groups, but the differences between the groups were not significant and were independent of time since the procedure.	Interesting study using bilateral legs in each patient as self control. Overall patient numbers were low (43) but 86 limbs treated. Change in laser use from pulsed to continuous part way through study means results (no difference in short-term outcome

Reference	Details of intervention/ anaesthetic used	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/ adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
								(98%) in the EVA with ligation group (N.S.). Groin recurrence was due to an incompetent SFJ/GSV (9%) and to incompetent tributaries (7%) in the EVA without ligation group and due to neovascularisation (12%) in the EVA with ligation group.	superficial thrombophlebitis (7% and 2%, N.S.). Wound complications occurred in four limbs in the EVA with ligation group (haematoma, n=2; dehiscence, n=1; superficial groin infection, n=1) but in none in the EVA group.		between groups) have to be treated with care.
Pronk 2010[96] The Netherlands 1 site Setting: Outpatient clinic	SFL/S of the GSV with local tumescent anaesthesia	EVLA of the GSV with local tumescent anaesthesia	130 legs in 121 patients. SFL/S n= 68; EVLA n= 62 legs	Primary varicose veins. CEAP ≥ C2; GSV and SFJ incompetence (reflux >0.5s on DUS); intrafascial length of at least 15cm from SFJ and GSV diameter 0.3-1.5cm	Pain; restarting of daily activities, work and sport; mobility and self care; anxiety	Local anaesthesia followed by Inversion stripping with a pin stripper OR 980-nm diode laser ablation, 100 J/cm + additional depending on diameter of GSV. Sclerotherapy of residual superficial veins after both treatments	Days 1,2,3,7,14 (QOL) and weeks 1,6 and months 6 and 12 for DUS	Recurrence (on DUS) at 1 year SFL/S n=10% (5/49); EVLA n=9% (5/56)	Significantly more pain in EVLA, days 7,10 and 14 (P<0.01; P<0.01; P=0.01) vs. SFLS. 2(3%) patients with post –op, bleeding in SFLS.3 (5%) patients with a thrombus at SFJ after EVLA at 1 week, all resolved. No major complications.	Significantly more hindrance in mobility in surgery grp at day 1, but then more hindrance in EVLT grp at days 7 and 10 (P<0.01; P=0.01); self care and daily activities at day 7 (P=0.03; P=0.01) in EVLA vs. SFLS	After 1 year, no significant difference in DUS recurrence between the groups. Useful comparator of the two procedures but methodology could be improved with investigator blinding to ensure unbiased interpretation of results.
Rasmussen 2010[93] Hospital setting	EVLA local tumescent anaesthesia	Surgical stripping Local anaestheis	EVLA N=69; Surgery N= 68	Symptomatic varicose veins and GSV incompetence (CEAP; C2-4, Ep, As, Pr). Inclusive of	Recurrence (DUS); QOL (AVVSS, SF36); VCSS	Tumescent LA. Surgery through a 4 to 6 cm incision in the groin, with flush division of the GSV and division of all tributaries behind the second level of division.. The GSV was	12 days; 1, 3, 6 months then 1 and 2 years (reported)	A total of 18 (26%) in EVLA and 25 patients (37%) in the surgery group, developed recurrent varicose	Technical failure occurred in three EVLA and two surgery patients, reflux in	VCSS, AVVSS and several domains of the SF36 quality of life score improved	Useful comparison of surgery and EVLA . A high number of

Reference	Details of intervention/ anaesthetic used	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/ adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
				patients having had previous saphenofemoral ligation. If bilateral both limbs treated.		then removed using a pin-stripper to just below the knee. EVLA under DUS guidance with a 980-nm diode laser using pulse mode and a power of 12 W. The GSV was cannulated percutaneously just below the knee. Ablation from 1-2cm below the SFJ on withdrawal.		veins (not significant between groups).	the anterior accessory GSV, the groin, thigh and calf perforators was found in six, two, four, and three EVLA patients, and in three, three, nine and six surgery patients.	significantly in both groups, improvements were seen in the domains bodily pain, vitality and social functioning ($p < 0.01$).Improvements in QOL and VCSS were still present after 2 years	recurrences that the author cannot explain. Results show little difference between groups.

9.6.2 Included RCTs evaluating RFA

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Almeida 2009[78] America 5 sites, Europe 1 site Setting not reported	RF ablation with Closure FAST device	EVLT	69 patients (87 veins) RF= 46 legs, EVLT=41 legs	Incompetent GSV, 18-80 years; reflux considered significant if flow reversal for more than 0.5 secs	Primary: Adverse events Secondary: vein occlusion by duplex US at 48hrs and 1 months and QoL	RFA: intraluminally placed Closure FAST device with a 7 cm heating element. Energy delivered at 120 degrees C in 20 second cycles. EVL: 980 nm wavelength in the continuous mode at 12W of power with a linear endovenous energy density of 80J/cm. After treatment, the limbs were wrapped with compression bandages and class II compression stockings. Bandages removed after 24-72 hours, stockings used for 2 weeks.	48 hours and 1 month	VCSC. Significant differences in VSSC scores at the 1 week and 2 week visits. RF group had significantly reduced scores compared with the EVLT group.	Postop pain: RFA reported significantly lower pain levels than the EVLT group at 48 hours (0.7 vs 1.9) and 1 week (0.2 vs 1.8) and 2 weeks (0.1 vs 1.2) $p<0.001$. Differences in pain levels did not reach statistical significance at 1 months. Postop ecchymosis-	QIVIQ. Changes in global QOL scores were better with RFA (Closure FAST) at 7 and 14 days after treatment	Study is limited by small sample size and short follow-up but provides useful information on comparative postoperative recovery between RFA and EVLT.

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
									statistically significant differences in ecchymosis between treatment groups (at 48 hrs 67% RFA no bruising vs 20% no bruising in the EVL group)		
Helmy ElKaffas 2011 [99] Egypt, 1site Hospital setting	RFA Tumescent anaesthesia	Surgical Stripping	RFA, N=90; Surgery, N= 90	SFJ and great saphenous reflux on DUS either in response to Valsalva manoeuvre or standing with manual compression and release	Achievement of primary occlusion (or failure) on DUS. Operative time; hospital stay; costs; short and mid-term complications.	RFA: Reverse Trendelenberg position, refluxing superficial vein was cannulated under US guidance or in some cases (n=5, 6%) with failed cannulation, using surgical cut down. Cannulation was at the most distal point of reflux. Tip of the RFA catheter placed 2cm distal to the SFJ or just distal to the epigastric orifice. Tumescent LA delivered with a 20 gauge spinal needle and US guidance. RF energy was applied, the catheter was gradually withdrawn with a slow infusion of heparinised saline. Surgery: Standard surgery with saphenofemoral high ligation and GSV stripping at ankle (44%) or knee (56%).	1 week, 1 month and 6 monthly for 2 years	84 (94.5%) RFA primary occlusion; 100% successful surgical removal GSV in surgery group. Recurrence, RFA, 12 patients, average time to recurrence = 23.3 months (95% CI 22.5-24.1). Surgery, 9 patients with an average time to recurrence of 23 months (95% CI 21.3-24.6)	Group A, no major complication, 9(10%) focal paraesthesia; 6(6.6%) thrombophlebitis; 12(13%) severe pain requiring analgesics; 1 patient haematoma. Group B, higher rate of complication; 1 patient iliofemoral DVT (1.1%); 3 (3.3%) severe groin infections that required parenteral antibiotics; 12(13.3%) groin haematoma;	No QOL results	Study showed fewer complications with RFA compared to surgery but slightly better efficacy for surgery. Cost data also included shows RFA more expensive (p=0.003).

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
									3(3.3%) paraesthesia of the groin; 18 (20%) haematoma of the saphenous fascial compartment		
Goode 2010[88] UK 1 site Hospital setting	EVLA GA	RFA GA	Total : 135 patients Included =62. 45 patients with unilateral disease (ULARA); N=23 RFA, N=22 EVLA. 17 patients with bilateral disease (BLARA), N=17 legs EVLA, N=17 legs RFA	GSV without significant tortuosity or diameter less than 12mm lying in the saphenous compartment not a more superficial tributary. Veins free of current or previous thrombophlebitis. CEAP 2-6Ep,As and reflux only Pr.	VAS for self assessment of pain, bruising and return to activity.QOL using AVVSS. Duplex ultrasound scans	All procedures carried out under GA. RFA and EVLA carried out under US guidance, both inserted into GSV through a sheath to 2cm bellow the SFJ. Biolitec laser used to deliver at least 80 J/cm energy (EVLA). For RFA the generator was set to a power of 23W. Varices were treated with phlebotomy.	DUS at 7-14 days and 6 months post-operatively.	Both RFA and EVLA resulted in occlusion rates of 95% at 10 days postoperatively.	In the BLARA group, RFA resulted in significantly less pain than EVLA on days 2-11 RFA also resulted in significantly less bruising than EVLA on days 3-9. There were no significant differences in mean post operative pain, bruising and activity scores in the ULARA group.	No statistical significant differences between legs pre-op randomised to different treatments o AVVSS. No significant differences at 6 months between patients who were randomised to different treatments on AVVSS	Study did not compare effectiveness but side effects of treatments. Small sample sizes and short follow-up limit the interpretation of the results.
Shepherd 2010[94] UK 1 site Hospital	Radiofrequency ablation (RFA) (using VNUS ClosureFAST)	Endovenous laser ablation (EVLA)	RFA, n=67; EVLA, n=64	Patients over 18 years of age with primary GSV incompetence	Post procedural pain and analgesia use after 3 days ; QoL (AVVQ & SF-	General anaesthesia; For both techniques, the GSV was cannulated at or as near as possible to the most distal point of venous reflux and the catheter tip was positioned 2 cm from SFJ under US guidance. Standard tumescent local anaesthesia was	3 and 10 days (pain) and 6 weeks after treatment	Results were similar, with 15 (37%) and 14 (41%) patients returning to work within 3 days, and 29 (71 %) and 24 (71%) returning	Postprocedural pain and analgesia use were significantly less in the RFA group in the	Improvements in QoL at 6 weeks were seen in both groups, although there were no significant differences	Useful study comparing RFA (less pain) and EVLA (similar QoL) for post-procedural outcomes mainly

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
setting					12&VCSS); return to normal activities and work; complications at 6 weeks	infiltrated along the length of the vein under US guidance; Segmental RFA, the first segment was treated with 2 RFA cycles, and the remainder of the vein was treated with one RFA cycle per 7-cm segment. Extrinsic pressure was applied over the vein during treatment cycles; EVLA: the laser was continually withdrawn delivering energy >60 J/cm to the vein wall, with a power setting of 11 W. Patients with varicosities were treated with concomitant phlebectomies using a standard technique (Oesch hook) and all phlebectomy sites were sutured with 6/0 polypropylene.Tumescent anaesthesia was not used for phlebectomy incisions.		to work within 7 days in RFA and EVLA groups respectively. Similar results for back to normal activities	first 3 days and in the first 10 days; complications: 2 major : one pulmonary embolus after RFA and one lymphatic leak after EVLA	between the two groups in AVVQ, VCSS or SF-12 in either the physical component or mental component score	pain and only as short follow-up
Subramonia 2010[95] UK 1 site Hospital setting	RFA (using VNUS ClosureFAST) GA	Conventional surgery GA	RFA, n=47; conventional surgery, n=41 (34/128 legs exclude)	18-70 years; GSV reflux (primary or recurrent) on duplex imaging and requiring surgery Duplex scan confirmed suitability for RFA; fit for a general anaesthetic; allowing ambulation after the procedure	Time to normal activities; intraoperative complications; duration of procedure; postoperative morbidity; time to return to driving; patient satisfaction and QoL	Both groups: a single SC prophylactic dose of low molecular weight heparin at the time of intervention; operations under general anaesthesia; phlebectomy hooks used with simultaneous avulsion of varicosities that had been marked before operation; RFA: With the patient in the reverse Trendelenburg position,the GSV was accessed percutaneously by the Seldinger technique and a 6- or 8-Fr FAST-CATHTM Haemostasis Introducer inserted; the VNUSClosure PLUS intravascular catheter with bipolar electrodes was introduced through the sheath and positioned in the GSV with its tip just below the entry of the superficial epigastric vein.The target temperature was set at 85°C. The ablation was commenced	1 and 5 weeks after treatment	Time to normal activities (3 days vs 12.5 days), work (10 days vs 18.5 days)and driving (4 days vs 7 days) RFA significantly shorter than conventional surgery; Duration of procedure: significantly shorter for conventional surgery; Patient satisfaction: (VAS score) significantly higher in RFA group (10 vs 8.5).	Complications: significantly higher rate of cutaneous sensory abnormalities in conventional surgery; Postoperative morbidity: pain in first week (VAS score 1.70 vs 4.00) p=0.001 and analgesic requirements (days 2 vs 10)p=0.011 were significantly less in the RFA	QoL (AVVQ data): significantly greater improvement after RFA	RFA patients experienced less pain and recovered more quickly as demonstrated by patient satisfaction and QoL scores. Study limited by short-term follow-up and patients, operators and researchers not blinded. Valuable RCT for short term outcomes of RFA.

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
						just distal to the entry of superficial epigastric vein and the catheter was pulled back at the rate of 1·5–2 cm per min for the first 3 cm and 2–3 cm per min for the remainder of the procedure; Conventional surgery: patient in the Trendelenburg position; through a skin-crease groin incision the SFJ was exposed and tributaries of the GSV were ligated and divided; the GSV was ligated and divided close to the SFJ (high ligation); a perforate–invagination (PIN) stripper was passed down the open distal end of the vein to emerge at knee level and the skin to retrieve the stripper. The vein was secured to the upper end of the stripper, which was retrieved by pulling it down to knee level and out of the exit wound, thus stripping the vein.			group in the first week post treatment		

9.6.3 Included RCTs evaluating sclerotherapy

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Figueiredo 2009[85] Brazil 1 site Outpatient clinic	Ultrasound – guided foam sclerotherapy	Surgical stripping Regional anaesthetic	Ultrasound guided foam therapy N=27 but average 2.1 sessions/patient Surgery N= 29	Primary varicose veins CEAP C5 Ep As Pr (healed venous ulcers). No previous treatment. 18-70 years	Venous clinical severity scores based on pain, oedema, inflammation, hyperpigmentation and lipodermatosclerosis.	Surgery: saphenofemoral or saphenopopliteal ligation combined with saphenous stripping and phlebectomy for varicose saphenous tributaries and ligation of incompetent perforating veins. All surgical procedures carried out under regional anaesthesia. Sclerotherapy : Injections of foam were made into the saphenous trunk using a 20-gauge needle. The accessory veins were cannulated	30 and 60 days post-op; then 6 months or 180 days	The mean venous clinical severity scores measured before and after 180 days were as follows: Surgery group - pain: before 1.97 standard deviation (SD) 0.19, 180 days 0.72 SD 0.53; oedema: before 1.66	No serious adverse events were associated with any of the treatments. Most frequent minor complication in the surgery is suture	No QOL results	Small sample size and and short follow-up.

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
					Treatment effectiveness (DUS).	and the incompetent perforating veins were injected using 22-gauge needles. A maximum of 10ml of foam was injected per session and sessions were repeated up to 3 times		SD 0.48, 180 days 0.55 SD 0.63; inflammation: before 1.55 SD 0.63, 180 days 0.72 SD 0.45. Foam sclerotherapy group - pain: before 1.81 SD 0.40, 180 days 0.56 SD 0.51; oedema: before 1.70 SD 0.47, 180 days 0.48 SD 0.64; inflammation: before 1.67 SD 0.68, after 0.89 SD 0.32. All scores showed statistically significant reductions in both patient groups. The saphenous vein had been obliterated, 180 days after treatment, in 78% of the surgery group, compared with 90% in the foam sclerotherapy group.	dehiscence (n=11). In sclerotherapy group: thrombus without drainage (n=15).		
Ouvry 2008[90] France 6 sites Phlebology centres	Standardised polidocanol foam (Aethoxysklerol 3% mixed with sterile air)	Liquid polidocanol(Aethoxyskerol 3%)	95 Foam= 47, liquid =48	GSV insufficiency, truncal diameter of between 4 and 8 mm, CEAP C2-C6. 18-80 years old	Primary: elimination of venous reflux in the saphenous trunk. Secondary: differences in length of occlusion, rate of recanalisatio	Patients were treated with a single echo-guided GSV injection of either FOAM (one part 3% polidocanol to 4 parts sterile air, DSS technique) or liquid. 2 ml injected for veins 4-6 mm diameter and 2.5 ml injected for veins 6-8ml diameter. Patients lay suprine during treatment. The injection was given at the junction between the upper and middle-third of the thigh. No compression was applied after treatment, only compression stocking	3 weeks after and then every 6 months for 2 years.	3 weeks: Elimination of saphenous reflux was successful in 40/47 foam pts and 17/48 liquid pts ($p<0.001$). The length of occluded vein was significantly longer in the foam group. At 2 years: no canalisation was 12%	AE data was reported for overall study population. Thrombophlebitis (2 pts); asthenia (1pt), headache (1 pt), pain (2 pts).	NR	Two year follow-up data from this study shows foam sclerotherapy is more effective than liquid at elimination of saphenous reflux. This study is limited by no blinding of

Reference	Details of intervention/ anaesthetic	Details of comparator/ anaesthetic	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
					n, adverse events	if secondary pain or inflammation developed.		(4 pts) in liquid group and 53% (25 pts) foam group. Pts lost to follow-up were counted as treatment failures.			outcome assessors and the reporting of AE data of total study population rather than by treatment group.
Rabe 2008[92] Germany 11 sites Private practice and hospital settings	Standardised polidocanol foam (Aethoxysklerol 3% mixed with sterile air)	Liquid Aethoxysklerol 3%	108 Foam = 55; Liquid= 53	Incompetent GSV with diameter <12mm measured in an upright position 3cm below the sapheno-femoral junction (SFJ), incompetent terminal valve, reflux duration of 1 second or more and refilling time measured by PPG <25 secs., reflux GSV from SFJ at least to the knee, CEAP C2-C5,Ep, AS, PR, age 18-70year. EXCLUSION: history of DVT, leg oedema, patent foramen ovale and migraine.	Primary: Elimination of venous reflux of duration of >0.5 second at a location 3 cm distal to the SFJ 3 mths post treatment. Secondary: occlusion of GSV 3cm and 25 cm distal to the SFJ by duplex US.,CIVIQ questionnaire	Standardised polidocanol foam was prepared using the EASY-FOAM kit. In the liquid group Aethoxyskelerol 3% was used. The maximum doses per treatment session were limited to 5ml foam and 4ml liquid. Venus duplex assessment was performed with the patient in the standing position and reflux assessed after a Valsalva manoeuvre. During treatment patients lay suprine to minimise the risk of syncope. An 18 G venipuncture catheter was inserted into the GSV under US. Injection was given slowly while the patient lay in the recumbent position. Only one injection per session was allowed to standardise treatment. Venous reflux was assessed 3cm below the SFJ and if this was still above 0.5sec further sclerotherapy was performed. 30mmHg thigh length stocking was applied and patients were asked to wear this for at least 8 hours a day for 14 days.	3 months following completion of the final sclerotherapy session. Duplex US and photoplethysmography	Elimination of venous reflux at 3 months: 69% foam vs 27% liquid (p<0.0001). Mean reflux time : Foam decreased from 3.4 to 1.1 sec vs 3.7 to 2.3 in the liquid group. Occlusion of GSV: foam 29 pts vs 9 liquid pts.(p<0.0001)The mean number of treatments was 1.3 in foam vs 1.6 in the liquid group.	No difference in adverse drug reactions was observed between groups (17 patients in foam group and 22 in liquid group). Most common AEs were: pain, haematoma, phlebitis or thrombophlebitis, pigmentation, dysthesia or paradysthesia	CIVIQ questionnaire. Patient satisfaction improved significantly more in the foam group	Although this study was limited by no blinding of patients, clinicians or assessors, it provides valuable safety data between these sclerotherapy methods. Longer follow-up data is needed.

9.6.4 Included RCT evaluating compression hosiery

Reference	Details of intervention	Details of comparator	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Houtermans-Auckel 2009[86] The Netherlands 1 site	Compression stockings	Control (no compression stockings)	Intervention, n=52; control, n=52	Complete incompetence of the GSV on duplex ultrasound and clinical stage C2 or C3 (clinical, etiologic, anatomic and pathophysiologic classification) venous disease; Excluded: those unable to wear elastic stockings, patients who already used elastic stockings, and patients with ulcers	Leg oedema; pain scores (VAS); postoperative complications; return to full activity	Crossectomy and short GSV inversion stripping using an InvisiGrip Vein Strippe (were performed on all patients. All patients were operated on as day surgery patients, 90% of whom were treated under spinal anaesthesia. Both patient groups underwent standard elastic bandaging selective compression of the proximal part of the GSV by a rolled gauze immediately postoperatively for 3 days. After this period, the control group did not wear elastic stockings. The intervention group were fitted with the class 2 medical compression stockings for which they had been measured preoperatively. The stockings provided an estimated compression of 23-32 mmHg (Venotrain compression stocking, type "Micro") patients were advised to wear them postoperatively for 4 weeks. They were advised to wear the stockings day and night for the first 2 weeks and then only during the day for the subsequent 2 weeks.	3 days, 2 weeks and 4 weeks postoperatively	The control group had a shorter duration of time off work (11 days (SD 7.5) compared with the intervention group (15 days (SD 8.4),p=0.02)	Leg Oedema: at 4 weeks a small but significant decrease in volume in the intervention group only; VAS (pain): no significant difference between groups; Postoperative complications: no difference between groups	NR	This study was limited by no blinding and stocking compliance in the intervention group was not measured. The study is of limited usefulness due to small sample size. Another limitation is the control group did not get an alternative/placebo (e.g. normal stockings).

9.6.5 Included RCT evaluating drugs

Reference	Details of intervention	Details of comparator	No. of patients	Patient inclusion criteria including type of varicose vein	Outcomes	Methods	Time of follow up	Results-efficacy Including recurrence	Results-complications/adverse events	Results-QoL(including scale used)	Interpretation of value of RCT for decision making
Martinez-Zapata 2008[89] Spain 32 sites	500mg capsules of calcium dobesilate for 3 months	Placebo capsules	Calcium dobesilate N= 246; placebo N= 263	CVD, CEAP grade 1 to 6; ≥18 years of age	Main outcome at 3 months: QoL. Oedema, CVD signs and symptoms; tolerance-safety of treatment; Secondary analysis of QoL added 9 months after the end of the treatment	Calcium dobesilate capsules twice daily or placebo twice daily for 3 months	3 months and 12 months	At 3 months no significant difference between groups (oedema, symptoms of CVD).	Similar adverse effects in placebo and intervention groups	At 3 months no significant difference between groups for the main outcome (QoL) (p =0.07). The secondary analysis suggested an improvement in QoL 9 months after the end of the treatment (p = 0.02).	RCT supported by the industry: no difference in the main outcomes at the end of the 3 months-treatment with calcium dobesilate.

9.7 STUDIES EVALUATING THE SAFETY OF VARICOSE VEIN TREATMENTS

Study	Type of study	Intervention	Number of patients (limbs)	Summary of Results	Comments
EVLT					
Van Den Bos (2009)[54]	Systematic review	EVLT	34 studies (clinical trials and case reports)	ecchymoses and pain frequently reported nerve injury, skin burns, DVT and pulmonary embolism seldom occur. 2 cases of device-related complications (foreign body from guide wire becoming loose during procedure)	An overview of studies on EVLT between 2001 and 2008
Fernandez (2008)[120]	Cohort observational	EVLT (810-nm diode laser) and phlebectomies	1559 patients (1985 ablations)	Pain and ecchymoses noted in most patients Superficial phlebitis (2.9%) Hyperpigmentation (4%) 2 DVT occurred (0.13%) Local transient paraesthesia at ankle and midcalf (2.43%) resolved after 2 weeks	Large cohort of patients with no major complications reported
Huisman (2009)[121]	Cohort observational	EVLT (810-nm laser) of the SSV	150 patients (169 limbs)	2 patients sural nerve paraesthesia (1.3%) 6 patients (6 limbs)superficial thrombophlebitis	EVLT of SSV rather than GSV. Short follow up at 6 weeks post procedure.
Rathod (2010)[122]	Prospective single centre single arm	EVLT using 1470-nm laser	72 patients (76 limbs)	Vein phlebitis, induration, haematoma (but self-limiting and did not require any active intervention or hospital admission). Pain, bruising and paraesthesia self-limiting Paraesthesia 10.53% of limbs after 1 month decreased to 2.63% limbs at 6 months Puncture site infection in 6.58% of limbs healed after a week of antibiotics No severe complications reported such as DVT,	Use of different wavelength laser reports similar safety data to standard laser therapy.

Study	Type of study	Intervention	Number of patients (limbs)	Summary of Results	Comments
				pulmonary embolism, skin burns, motor nerve lesions	
RFA					
Creton (2010)[123]	Prospective multicentre single arm	RFA using ClosureFast catheter	225 patients (295 limbs)	haematomas (1.4%), ecchymoses (5.8%), paresthesia (3.4%) pigmentations (3.1%) and superficial venous thrombosis (1%) of limbs no serious complications	One year follow-up.
SCLEROTHERAPY					
Gillet (2008)[124]	Prospective, multicentre, controlled study	Foam sclerotherapy (0.5% to 3% concentration))	818 GSV, 207 SSV were treated in 1025 patients	1 case septicaemia 1 case transient ischaemic attack 5 symptomatic DVT (0.5%) 5 asymptomatic DVT (0.5%) 1 pulmonary embolism 0.07%) 8 cases migraine (0.78%) 7cases of isolated visual disturbance(0.68%) 12 cases chest pressure (1.17%)	Overall venous thromboembolic events were 1.07%
Blaise (2010)[79]	RCT	Foam sclerotherapy 1% vs 3%	143 patients	No significant differences between the groups Main AEs pain, superficial thrombosis, pigmentation, matting, induration and cutaneous inflammation. 3 thromboembolic complications altogether (2 in 1% treatment, 1 in 3% treatment group) Pigmentation remained in 4% to 9 % of patients at 3 year follow-up.	This study shows pigmentation can remain at 3 years post sclerotherapy.

Study	Type of study	Intervention	Number of patients (limbs)	Summary of Results	Comments
Ma (2010)[126]	Case study	Foam sclerotherapy	3 patients	Clot embolism post foam sclerotherapy induced right middle cerebral artery stroke 2 days post procedure Gas embolism stroke occurred immediately post foam sclerotherapy No cause detected in third patient with stroke occurring one day post EVLT and foam sclerotherapy	All 3 patients had patent foramen ovale All 3 patients recovered completely within a few days.
SURGERY					
Rudstrom (2007)[127]	Systematic review	Open varicose vein surgery	81 patients (87 cases)	Laceration or division of the femoral vein dominated venous injuries (28/43). Partial stripping of the femoral vein not common (4/43) Arterial stripping predominated in arterial injuries (17/44) Major arterial complications resulted in ischemia. These often had associated diagnostic delay with poor reconstruction results. Only 30% (13/44) of arterial injuries were detected peroperatively. Amputation rate 34% (15/44), rising to 100% when combined with intra-arterial sclerotherapy (5/5 cases). When stripping an artery below the femoral artery, the amputation rate was high (42%; 5/12) and morbidity severe (85%; 11/12). All fatal injuries (5 cases) were venous.	A systematic review of latrogenic vascular injuries occurring during varicose vein surgery.Such injuries are rare but serious. The papers included were of case series and case report design.
Van Rij 2008128	RCT	Polytetrafluoroethylene patch as a mechincal suppressant of angiogenesis at the SFJ	292(389 limbs) Patch = 142;(194 limbs)	There was a highly significant reduction in the incidence of ultrasound-detectable SFJ recurrence with the difference remaining at 3 year follow-up (16.3% versus 37.6%; $p<0.0001$)	The patch halved the recurrence rate to 3 years postoperatively in clinical subgroups Not all neovascularisation

Study	Type of study	Intervention	Number of patients (limbs)	Summary of Results	Comments
			Control=150 (195 limbs)		was prevented by the patch
Heim and De Maeseneer 2008[129]	Prospective single centre single arm Study group compared with historical control group	GSV stump completely resected and closed with an inverting suture (group B) Historical control (group A) conventional flush SFJ ligation	Trial group B: 45 patients (65 limbs) Historical group A; 48 patients (70 limbs)	The technique of resecting the GSV stump completely, instead of simpler flush ligation, did not decrease postoperative neovascularistion or improve two year clinical results	Results are observational

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KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
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3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
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7. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
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9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
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11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
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20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
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26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
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32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
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