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Endovenous interventions on varicose veins of the leg

Nelzén O, Cervin A, Daxberg E-L, Drott C, Gelin J, Persson J, Samuelsson O, Svanberg T, Jivegård L.

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Endovenous interventions on varicose veins of the leg [Endovenösa interventioner mot åderbråck]

Nelzén O[1*], Cervin A[2], Daxberg E-L[4], Drott C[3], Gelin J[5], Persson J[6], Samuelsson O[6], Svanberg T[4], Jivegård L[6].

[1] Vascular Surgery Unit, Skaraborg Hospital Skövde, Sweden
[2] Vascular Surgery Unit, North Älvsborg Hospital, Trollhättan, Sweden
[3] Vascular Surgery Unit, South Älvsborg Hospital, Borås, Sweden
[4] Medical Library, Sahlgrenska University Hospital, Göteborg, Sweden
[5] Dept of Vascular Surgery, Sahlgrenska University Hospital, Göteborg, Sweden
[6] HTA-centrum, Region Västra Götaland, Sweden

[*]Corresponding author

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1. Abbreviations

CS	Conventional surgery
DVT	Deep venous thrombosis
EVLA	Endovenous laser ablation
HRQoL	Health related quality of life
IQR	Inter-quartile range
NCGC	National Clinical guidance Centre
PE	Pulmonary embolism
PCS	Physical component score (of SF-36)
PP	Per protocol
QALY	Quality Adjusted Life Year
RCT	Randomised clinical trial
RFA	Radiofrequency ablation
SSV	Small saphenous vein
UGFS	Ultrasound guided foam sclerotherapy
VCSS	Venous clinical severity score

2. Summary of the Health Technology Assessment

Background
Venous insufficiency in the legs is caused by leaking valves in the main venous trunks leading to venous hypertension in the standing position. Invasive interventions may be needed for insufficient superficial veins, varicose veins, due to complications such as oedema, itching and ultimately leg ulcers. Most often the prevalence of varicose veins is reported between 20 and 40% in the adult population and although there is no gender difference women more often seek medical advice for varicose veins. Approximately 1300 patients were treated invasively for symptomatic varicose veins in Region Västra Götaland during 2014. Today, the majority of interventions are carried out as outpatient surgery using surgical techniques and general anesthesia. Endovenous methods for treatment of varicose veins include several percutaneous techniques, mainly endothermal ablation of truncal veins using radiofrequency ablation (RFA) or endovenous laser ablation (EVLA) and ultrasound guided foam sclerotherapy (UGFS). Endovenous techniques do not require an operating theatre or general anaesthesia. Recent data from the UK show that endothermal ablation presently constitutes 31% of all invasive treatments for varicose veins. There are no recent such national data from Sweden.

Question at issue
Are endovenous techniques better than open surgery for adult patients with symptomatic lower limb varicose veins with truncal reflux regarding health related quality of life, symptomatic recurrences, time to return to work and postoperative complications?

Main results
We identified the most recent relevant systematic review (NICE guidance, 2013) and searched for relevant articles published subsequent to the NICE guidance. Forty-one articles were sent to the participants of the project group for possible inclusion and 22 articles, including the NICE guidance were selected: two systematic reviews, seven RCTs and 13 case series; one of the SRs was only commented upon.
Case series were only used for risks and complications.
It was decided to accept the assessment of the quality of evidence (GRADE) in the NICE guidance. We graded the quality of evidence for outcomes reported in the RCTs published after the NICE guidance and finally combined the two gradings. Results of EVLA and RFA are presented together as results of endothermal ablation.

<u>Endothermal ablation compared with surgery</u>
Critical outcomes: There may be little or no difference in HRQoL one year after endothermal ablation compared with surgery (GRADE ⊕⊕◯◯). No studies reported symptomatic recurrence.
Important outcomes: There may be little or no difference in the rate of reflux at short-term and medium-term follow-up and in the symptom score VCSS during long-term follow-up after endothermal ablation compared with surgery (GRADE ⊕⊕◯◯). Time to return to work may be slightly shorter after endothermal ablation compared with surgery (GRADE ⊕⊕◯◯). There may be little or no difference in postoperative pain after endothermal ablation compared with surgery (GRADE ⊕⊕◯◯).

Ultrasound guided foam sclerotherapy (UGFS) compared with surgery
Critical outcomes: There is probably little or no difference in HRQoL one year after UGFS compared with surgery (GRADE ⊕⊕⊕◯). No studies reported symptomatic recurrence.
Important outcomes: There is probably a higher rate of reflux at one and three years after UGFS compared with surgery (GRADE ⊕⊕⊕◯). It is uncertain whether there is any difference in time to return to work after foam sclerotherapy compared with surgery (GRADE ⊕◯◯◯). Ultrasound guided foam sclerotherapy may be associated with less postoperative pain compared with surgery (GRADE ⊕⊕◯◯). There may be little or no difference in the symptom score VCSS at long-term follow-up after UGFS compared with surgery (GRADE ⊕⊕◯◯).

Ultrasound guided foam sclerotherapy compared with endothermal ablation
Critical outcomes: There is probably little or no difference in HRQoL one year after foam sclerotherapy compared with endothermal ablation (GRADE ⊕⊕⊕◯). No study reported data on symptomatic recurrence.
Important outcomes: Foam sclerotherapy is probably associated with a higher rate of truncal reflux at one year compared with endothermal ablation (GRADE⊕⊕⊕◯). There is probably little or no difference in the symptom score VCSS during follow-up until three years after UGFS compared with endothermal abliation (GRADE⊕⊕⊕◯). There may be little or no difference in post-operative pain after foam sclerotherapy compared with endothermal ablation (GRADE ⊕⊕◯◯). It is uncertain whether there is any difference in time to return to work after foam sclerotherapy compared with endothermal ablation (GRADE⊕◯◯◯).

Concluding remarks
During 2014, approximately 1300 patients in Region Västra Götaland underwent invasive interventions for symptomatic varicose veins. Today, conventional surgery, as outpatient surgery, in general anaesthesia is used for most patients with varicose veins. Endovenous treatment modalities include endothermal ablation and ultrasound guided foam sclerotherapy (UGFS) and require no operating theatre or general anaesthesia. The use of endovenous techniques can free operating theatre resources, but are not always applicable. Endothermal ablation procedures constituted approximately 25% of all invasive interventions for symptomatic varicose veins during 2014 in Region Västra Götaland. Results of endothermal ablation may be similar to those of surgery at short- and medium-term follow-up. The results of endovenous techniques are promising but the critical outcome symptomatic recurrence is not studied and long-term (5 – 10 years) results are lacking. Severe adverse events are rare. The frequency with which endovenous techniques can be used for primary and secondary treatment of patients with symptomatic varicose veins is not defined, but can be estimated to approximately 40%. Health economic analyses show uncertain but probably small differences in costs and benefits between the techniques.

3. Svensk sammanfattning – Swedish summary

Bakgrund
Venös insufficiens i benen orsakas ofta av insufficienta klaffar i de ytliga venerna vilket leder till venös hypertension vid stående. Vid åderbråck till följd av ytlig venös insufficiens kan hos en mindre andel av patienterna invasiv åtgärd behövas för att behandla komplikationer som bensvullnad, klåda och slutligen bensår. Prevalensen av åderbråck hos vuxna anges ofta till 20 – 40%, utan könsskillnader, men kvinnor söker oftare vård för åderbråck. Under 2014 genomfördes cirka 1300 interventioner för symtomgivande åderbråck i VGR. Merparten av ingreppen utförs idag som dagkirurgiska ingrepp med kirurgiska metoder i generell anestesi. Endovenösa tekniker för åderbråck inkluderar olika minimal-invasiva perkutana tekniker, främst endotermal ablation (med radiofrequency, RFA eller laser, EVLA) samt ultraljudsledd skumsklerosering (UGSF). Dessa metoder kräver ej operationssalsresurser eller generell anestesi, men är ej alltid tillämpliga. I Storbritannien visar aktuella siffror att 31% av invasiva åtgärder för åderbråck idag utförs med endotermal ablation.

Frågeställning
Är de endovenösa teknikerna bättre än öppen kirurgi för vuxna med symtomgivande åderbråck i benen på grund av huvudstamsreflux vad gäller hälsorelaterad livskvalitet, symtomgivande återfall, sjukskrivningstid och postoperativa komplikationer?

Resultat
Vi identifierade den senast publicerade systematiska översikten NICE guidance, 2013) och sökte efter relevanta artiklar publicerade efter sista sökdatum i denna. Fyrtioen artiklar lästes av projektgruppen för eventuell inkludering och 22 artiklar, inklusive NICE guidance, valdes ut: två systematiska översikter (SR), inklusive NICE guidance, varav en enbart kommenterades. Därtill sju RCT:er och 13 fallserier. Fallserierna användes för redovisning av risker och komplikationer. Vi beslutade att acceptera bedömningen av evidensstyrka (GRADE) i NICE guidance och genomförde sedan GRADE på de senare publicerade RCT:erna. Till sist gjordes en sammanvägd GRADE. Resultaten för RFA och EVLA presenteras gemensamt som resultat av endotermal ablation.

<u>Endotermal ablation jämfört med kirurgi</u>
Kritiska utfall: Det kan vara liten eller ingen skillnad i hälsorelaterad livskvalitet (HRQoL) ett år efter endotermal ablation jämfört med kirurgi (GRADE ⊕⊕◯◯). Ingen studie redovisade symtomgivande återfall.
Viktiga utfall: Det kan föreligga liten eller ingen skillnad vad gäller förekomsten av huvudstamsreflux på kort och medellång sikt efter endotermal ablation jämfört med kirurgi (GRADE ⊕⊕◯◯). Sjukskrivningstiden kan vara något kortare efter endotermal ablation jämfört med kirurgi (GRADE ⊕⊕◯◯) och det kan finnas en liten eller ingen skillnad vad gäller postoperativ smärta (GRADE ⊕⊕◯◯). Det är osäkert huruvida det föreligger någon skillnad i symtomscoren VCSS tre till fem år efter endotermal ablation jämfört med kirurgi (GRADE ⊕◯◯◯).

Ultraljudsledd skumsklerosering (UGFS) jämfört med kirurgi
Kritiska utfall: Det är troligen liten eller ingen skillnad i HRQoL ett år efter UGFS jämfört med kirurgi (GRADE ⊕⊕⊕◯). Ingen studie redovisade symtomgivande återfall.
Viktiga utfall: Det föreligger troligen betydligt oftare huvudstamsreflux (26,4 - 28,3% vs 6,5 - 15%) ett till tre år efter UGFS jämfört med kirurgi (GRADE ⊕⊕⊕◯). Det är osäkert huruvida det föreligger någon skillnad i sjukskrivningstid efter UGFS jämfört med kirurgi (GRADE ⊕◯◯◯). Ultraljudsledd skumsklerosering kan ge mindre postoperative smärta jämfört med kirurgi (GRADE ⊕⊕◯◯). Det kan vara liten eller ingen skillnad i symtomscoren VCSS vid långtidsuppföljning efter UGFS jämfört med kirurgi (GRADE ⊕⊕◯◯).

Ultraljudsledd skumsklerosering jämfört med endotermal ablation
Kritiska utfall: Det är troligen liten eller ingen skillnad i HRQoL ett år efter UGFS jämfört med endotermal ablation (GRADE ⊕⊕⊕◯). Ingen studie redovisade symtomgivande återfall.
Viktiga utfall: Det föreligger troligen oftare huvudstamsreflux ett till tre år efter UGFS jämfört med endotermal ablation (GRADE⊕⊕⊕◯). Det är troligen liten eller ingen skillnad i symtom-scoren VCSS upp till tre år efter UGFS jämfört med endotermal ablation (GRADE⊕⊕⊕◯). Det kan finnas en liten eller ingen skillnad i postoperativ smärta efter UGFS jämfört med endotermal ablation (GRADE ⊕⊕◯◯). Det är osäkert huruvida det är någon skillnad i sjukskrivningstid efter UGFS jämfört med kirurgi (GRADE ⊕◯◯◯).

Sammanfattande synpunkter
Symtomgivande åderbråck är vanligt och 2014 behandlades cirka 1300 patienter i VGR invasivt för åderbråck. Kirurgisk åtgärd i generell anestesi, oftast som dagkirurgi, används idag för flertalet av dessa patienter. Endovenösa behandlingstekniker, inkluderande endotermal ablation med radiofrequency (RFA) eller laser (EVLA) samt ultraljudsledd skumsklerosering fordrar ej operationssalsresurser eller generell anestesi men är ej alltid tillämpliga. Endotermal ablation utgjorde 2014 ungefär 25% av invasiva interventioner för symtomgivande åderbråck i VGR. Det finns ett begränsat vetenskapligt stöd för att resultaten efter endotermal ablation upp till tre år är relativt lika resultaten efter kirurgi, men det kritiska utfallet symtomgivande återfall är ej studerat. Ultraljudsledd skumsklerosering är den billigaste tekniken men är förknippad med högre frekvens av huvudstamsreflux än kirurgi och endotermal ablation. Endovenösa tekniker visar lovande resultat vid kort och medellång uppföljning och kan frigöra operationssalsresurser men vissa kritiska utfall som symtomgivande återfall saknas, liksom långtidsresultat (5 – 10 år). Allvarliga biverkningar är relativt sällsynta. Andelen patienter som är aktuella för primär eller sekundär åtgärd för symptomgivande åderbråck och som kan behandlas med endovenösa åtgärder är inte definierad, men kan uppskattas till cirka 40%. Hälsoekonomiska analyser visar osäkra men troligen små skillnader i kostnad och patientnytta mellan teknikerna.

The above summaries were written by HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. The Regional Health Technology Assessment Centre (HTA-centrum) Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary addresses the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2015-03-25

Christina Bergh
MD, Professor
Elisabeth Hansson-Olofsson
PhD, Senior lecturer
Magnus Hakeberg
OD, Professor
Lennart Jivegård
MD, Senior university lecturer
Jenny Kindblom
MD, Associate professor

Anders Larsson
MD, PhD
Christian Rylander
MD, PhD
Ola Samuelsson
MD, Associate professor
Ninni Sernert
Associate professor
Henrik Sjövall
MD, Professor

Petteri Sjögren
DDS, PhD
Maria Skogby
RN, PhD
Annika Strandell
MD, Associate professor
Therese Svanberg
HTA-librarian

4. Summary of Findings (SoF-table)

Endothermal ablation (Radiofrequency ablation; RFA, or Endovenous laser ablation; EVLA) versus conventional surgery for varicose veins (PICO 1).

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE[1]
HRQoL (SF-36, EQ-5D, AVVQ, CIVIQ)	1 SR (5 RCTs) + 3 RCTs	No significant intergroup differences at one and three years	No significant intergroup differences at one and three years	⊕⊕◯◯ Low[2]
Presence of reflux	1 SR (6 RCTs) + 3 RCTs	RR = 1.16 Non-significant	1.4 % to 5.6 % Non-significant	⊕⊕◯◯ Low[3, 4]
Time to return to work	**RFA** 1 SR (2 RCTs)		- 9 days (95 % CI: -11.6 to – 5.6)	⊕⊕◯◯ Low[2]
	EVLA 1 SR (2 RCTs)		- 0.2 days Non-significant	⊕⊕◯◯ Low[2]
Postoperative pain	1 SR (4 RCT) + 1 RCT		- 0.2 (VAS 0-10) Non-significant	⊕⊕◯◯ Low[5]
Venous clinical severity score	1 SR (1 RCT) + 2 RCTs		-0.3 (95% CI: -1.63 to +0.27)	⊕◯◯◯ Very low[6]

Abbreviations. RR = risk ratio. CI = confidence interval.

Footnotes:

[1] The quality of evidence for outcome variables that have been reported in new RCTs published later than the last literature search date of the NICE report is a weighted consensus rating based on both the NICE report and the new RCTs. For outcome variables only reported in the RCTs included in the NICE report the grading in their report was accepted.

[2] The quality of evidence was downgraded two steps for serious study limitations, some uncertainty for directness and uncertainty for precision.

[3] The quality of evidence was downgraded two steps for serious study limitations, some inconsistency, some uncertainty for directness and uncertainty for precision.

[4] The grading in the NICE report was ⊕◯◯◯(Very low). The new RCTs were of higher quality and added more patients. Therefore, the final grading was increased to ⊕⊕◯◯(Low).

[5] The grading in the NICE report was ⊕◯◯◯(Very low). The new RCT was of high quality with only some indirectness. Therefore, the final grading was increased to ⊕⊕◯◯(Low).

[6] The quality of evidence was downgraded three steps for serious study limitations, very serious indirectness and uncertainty for precision.

Summary of Findings (SoF)
Foam sclerotherapy versus conventional surgery for varicose veins (PICO 2).

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE[1]
HRQoL (SF-36, EQ-5D, AVVQ, CIVIQ)	1 SR (2 RCTs) + 2 RCTs	No significant intergroup differences at one and three years	No significant intergroup differences at one and three years	⊕⊕⊕◯ Moderate[2]
Presence of reflux	1 SR (4 RCTs) + 2 RCTs	RR = 2.49 p < 0.01	13.3% − 19.9%	⊕⊕⊕◯ Moderate[2]
Time to return to work	1 SR (1 RCT)		- 1.4 days Non-significant	⊕◯◯◯ Very low [1]
Postoperative pain	1 SR (2 RCTs)	Presence of pain RR = 0.32 (95 % CI: 0.20 to 0.50)	VAS scale - 0.7 (VAS 0 – 10) (95 % CI: -0.2 to -1.2)	⊕⊕◯◯ Low[3]
Venous clinical severity score	1 SR (1 RCT) + 1 RCT	No significant intergroup differences at three and five years	No significant intergroup differences at one and three years	⊕⊕◯◯ Low[3]

Abbreviations: RR = risk ratio. CI = confidence interval.
Footnotes:
[1] The quality of evidence for outcome variables that have been reported in new RCTs published later than the last literature search date of the NICE report is a weighted consensus rating based on both the NICE report and the new RCTs. For outcome variables only reported in the RCTs included in the NICE report the grading in their report was accepted.
[2] The quality of evidence was downgraded one step for some study limitations and uncertainty regarding precision
[3] The quality of evidence was downgraded two steps for serious study limitations and serious indirectness.

Summary of Findings (SoF)
Endothermal ablation (Radiofrequency ablation; RFA, or Endovenous laser ablation; EVLA) versus foam sclerotherapy for varicose veins (PICO 3)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE[1]
HRQoL (SF-36, EQ-5D, AVVQ, CIVIQ)	1 SR (1 RCT) + 3 RCTs	No significant intergroup differences	No significant intergroup differences	⊕⊕⊕◯ Moderate[2]
Presence of reflux	1 SR (1 RCT) + 3 RCTs	RR = 0.29 (95 % CI: 0.20 to 0.42)	-27.9 % to – 11.5 %	⊕⊕⊕◯ Moderate[2,3]
Postoperative pain	1 SR (1 RCT)	No significant intergroup differences	VAS scale (VAS 0 – 10) 1.0 for EVLA (95% CI: -0.5 to 1.5) -0.4 for RFA (95% CI: -0.8 to 0.1	⊕⊕◯◯ Low
Venous clinical severity score	1 SR (1 RCT) + 2 RCTs		No significant intergroup differences at three months and three years	⊕◯◯◯ Very low[4]

Abbreviations. RR = risk ratio. CI = confidence interval.
Footnotes:
[1] The quality of evidence for outcome variables that have been reported in new RCTs published later than the last literature search date of the NICE report is a weighted consensus rating based on both the NICE report and the new RCTs. For outcome variables only reported in the RCTs included in the NICE report the grading in their report was accepted.
[2] The quality of evidence was downgraded one step for some study limitations and uncertainty regarding precision
[3] The grading in the NICE report was ⊕⊕◯◯(Low).. The new RCTs were of higher quality and added more patients. Therefore, the final grading was increased to ⊕⊕⊕◯(Moderate).
[4] The quality of evidence was downgraded three steps for serious study limitations, very serious indirectness and uncertainty for precision.

Quality of evidence

High quality ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality ⊕⊕⊕◯	We aremoderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

5. Participants in the project.

Who posed the question?
Ulf Angerås, MD, Associate professor, Regional Advisory Board for Priority Setting (Region Västra Götaland).

Participants in the HTA group from the clinical departments
Olle Nelzén, MD, associate professor, The Unit of Vascular Surgery, Skaraborg hospital Skövde,
Anne Cervin, MD, The Unit of Vascular Surgery, Trollhättan
Christer Drott, MD, associate professor, The Unit of Vascular Surgery,
South Älvsborg hospital, Borås
Johan Gelin, MD, associate professor, The Department of Vascular Surgery, Sahlgrenska University Hospital, Göteborg

From the HTA-centrum
Lennart Jivegård, MD, Senior university lecturer, HTA-centrum, Region Västra Götaland
Ola Samuelsson, MD, Associate professor, HTA-centrum, Region Västra Götaland
Therese Svanberg, HTA-librarian, Medical Library, Sahlgrenska University Hospital, Göteborg
Eva-Lotte Daxberg, Medical Library, Sahlgrenska University Hospital, Göteborg
Josefine Persson, Health economist, Gothia Forum, Göteborg

External reviewers
Margareta Hellgren, Professor, senior consultant, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Göteborg
Magnus Rizell, Consultant surgeon, Transplantation unit, Sahlgrenska University Hospital, Göteborg

Are there any conflicts of interest for the proposer or any of the participants in the work group?
No

Project time

HTA was accomplished during the period of 2014-05-28 – 2015-03-25.
Last search updated in June 2014.

6. Varicose veins

Venous insufficiency of the legs is caused by insufficient valves in the veins which leads to venous hypertension in the upright position. There are no commonly accepted effective invasive interventions for deep venous insufficiency. Regarding the superficial veins, insufficient valves often cause visible varicose veins and may induce symptoms such as oedema, skin pigmentation, itching, lipodermatosclerosis, and ultimately in some patients leg ulcers. Symptoms from the venous congestion include a feeling of heaviness, fatigue and pain from tense varices. Whether diffuse aching, restless legs and muscle cramps are caused by venous insufficiency is unproven and a matter of debate. Symptomatic varicose veins may lead to disability and an impaired HRQoL.

This analysis does not include minor venules (< 0.3 cm in diameter) or spider veins.

Prevalence and incidence

The prevalence of varicose veins depends on the definition, age span and method of investigation. Prevalence figures ranging between 1 and 73 % have been reported. Most investigators have reported a prevalence between 20 and 40 %. Thus, approximately every third adult will develop varicose veins. The prevalence increases with age and although there is no gender difference, women tend to seek medical advice for varicose veins more often than men. Therefore, more interventions for varicose veins are performed in women.

Present treatment

Since the late 1990s, Region Västra Götaland has guidances with criteria for when invasive interventions on varicose veins are reimbursed by Region Västra Götaland. “Cosmetic” indications are excluded from public funding. In short, the criteria for intervention are main stem (truncal) insufficiency (great and/or small saphenous veins) or other pathology causing axial venous insufficiency that leads to venous hypertension. Truncal insufficiency and reflux is demonstrated by ultrasound. The majority of varicose vein interventions are carried out by vascular or general surgeons. Today, the majority of the interventions are carried out as outpatient surgery using conventional open surgical techniques and general anesthesia. Two hospitals in Region Västra Götaland have adopted endovenous methods, South Älvsborg hospital (SÄS) and North Älvsborg hospital (NÄL). There are also a few private clinics that use these endovenous methods.

Number of patients per year who are treated surgically or endovenously for varicose veins

In Region Västra Götaland, approximately 1300 invasive interventions for varicose veins were performed during 2014. The number of varicose vein interventions (endovenous and surgical respectively) in the major hospitals in Region Västra Götaland 2014 was 0 and 8 (Sahlgrenska University Hospital), 77 and 171 (North Älvsborg hospital), 115 and 129 (South Älvsborg Hospital) and 0 and 313 (Skaraborg Hospital). In total 813 invasive interventions in the major hospitals, 24% of the interventions were endothermal ablations. Skaraborg county in Region Västra Götaland has had stable waiting lists for varicose vein interventions. Based on 313 reported invasive interventions for symptomatic varicose veins during 2014 in Skaraborg County, approximately 120 patients per 100.000 inhabitants may need an invasive intervention for varicose veins.

The normal pathway through the health care system

The pathway varies between centres. There is consensus that an ultrasound examination is mandatory before the decision to perform an intervention is made. A “one-stop outpatient clinic” for primary referrals, where ultrasound and clinical examination could be performed at the same visit, is often recommended.
There is significant variation in Region Västra Götaland regarding the time spent on the waiting list between decision and intervention. Ideally, the surgeon who makes the initial clinical assessment also should operate the patient. However, this goal is often not achieved.

Actual waiting time in days for treatment

Currently, the average waiting time for a complete clinical examination (including duplex assessment) at e.g. Skaraborg Hospital Skövde is 76 days (39 days for duplex and 37 days for clinical assessment). After that, the average waiting time to surgery is 59 days. At South Älvsborg hospital (SÄS), the corresponding waiting times are 30 days and 30 days respectively. For North Älvsborg hospital, 72% are reported to receive treatment within 90 days.

7. Endovenous interventions on varicose veins

Endovenous methods to treat varicose veins include a variety of techniques that all aim to close veins through minimal-invasive percutaneous access. These methods include thermal, chemical and mechanical techniques. All these methods have been introduced mainly during the late nineties and the documentation of their efficacy and safety is still limited. Radiofrequency ablation (RFA) and endovenous laser ablation (EVLA), both of which are thermal techniques differing with respect to the way energy is delivered to the treatment catheter, and ultrasound guided foam sclerotheraphy (UGFS) are presently the best documented endovenous methods.

All endovenous methods require the use of duplex ultrasound to guide the treatment and the interventionist must be trained in using duplex ultrasound as well as the treatment modality. The thermal methods require local tumescent anesthesia whereas UGFS does not. Visible local varicosities cannot be treated with endothermal techniques, but are usually treated by phlebectomy surgical stab incisions or with UGFS. An advantage of UGFS is that it can be used without the use of anesthesia.

Endovenous interventions have potential advantages compared with conventional surgical techniques. They do not require an operating theatre and general anesthesia. The risk of general anaesthesia in patients undergoing varicose vein surgery is negligible. The postoperative pain may be less after an endovenous intervention, and the need for post-operative sick leave may be shorter. Furthermore, if the interventions are made outside of the operating ward the need for personnel is reduced. Under such circumstances all these endovenous methods may be associated with lower costs than open surgery. Futhermore, patients usually prefer less invasive treatments.

The drawbacks of endothermal interventions include the costs for the generator and that each catheter for RF and laser can be used for one patient only. Furthermore, additional portable colour-duplex machines are needed, and the surgeons must be trained to use them adequately.

The central question for the current HTA project

Are endovenous techniques better than open surgery for adult patients with symptomatic lower limb varicose veins with truncal reflux regarding health related quality of life, symptomatic recurrences, time to return to work and postoperative complications?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO 1	PICO 2	PICO 3
P = Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb	P = Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb	P = Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb
I = Endothermal ablation	I = Foam sclerotherapy	I = Foam sclerotherapy
C = Conventional surgery	C = Conventional surgery	C = Endothermal ablation
O = Critical Health related quality of life (measured with validated scales) Symptomatic recurrence Important but not critical Presence of reflux Time to return to work Postoperative pain Clinical status (measured with validated scales)	O = Critical Health related quality of life (measured with validated scales) Symptomatic recurrence Important but not critical Presence of reflux Time to return to work Postoperative pain Clinical status (measured with validated scales)	O = Critical Health related quality of life (measured with validated scales) Symptomatic recurrence Important but not critical Presence of reflux Time to return to work Postoperative pain Clinical status (measured with validated scales)

8. Review of Quality of Evidence

During June 2014 two librarians (TS, ELD) performed systematic searches in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were also scrutinized for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, selected studies and independently of one another assessed the obtained titles and abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the HTA project group, who read the articles independently and then decided in a consensus meeting which articles should be included in the final assessment.

This report is based on the NICE guidance, 2013, *Varicose veins in the legs* (published in July 2013), a systematic review (SR) with last literature search date 2012-10-17. The present literature search searched for studies published after 2012-10-17 identified a total of 772 articles (after removal of duplicates). The librarians excluded 711 articles after reading their titles and abstracts. Another 20 articles were excluded by the librarians after reading the articles in full text. Forty-one articles were sent to the participants of the project group and 22 articles (including the NICE guidance, 2013) were finally included in the report: two SR (one was critically appraised and one only commented upon under 11. Economic aspects), seven RCTs and 13 case series. Case series were only used for risks and complications.

The included studies are presented in Appendix 2. The RCTs have been critically appraised using modified checklists from SBU (Swedish Council on Health Technology Assessment) for randomized controlled trials. The NICE guidances were critically appraised using the AMSTAR checklist for systematic reviews. Excluded articles are listed in Appendix 3. The certainty of evidence was rated according to the GRADE system.

The present knowledge of endovenous interventions on varicose veins

Twenty-two articles were finally included: two SR (one was only commented upon), seven RCTs and 13 case series. The results of EVLA and RFA were combined as results of endothermal ablation, except if there was a clear difference in results for an outcome. Different HRQoL instrument were used, but the results are presented together. Generic HRQoL instruments included SF-36 and EQ-5D and disease-specific instruments included Aberdeen Varicose Vein Questionnaire (AVVQ) and the Chronic Venous Insufficiency Questionnaire (CIVIQ-2).

When outcomes (except for postoperative outcome) were reported after different lengths of follow-up, the data for the longest follow-up was used for conclusions and grading. The systematic review from NICE had high quality, and it was decided to accept its assessments of the certainty of evidence (GRADE). They were used as the start of the grading of the certainty of evidence in the present HTA. After the grading of the RCTs published after October 17, 2012, we finally combined the two assessments of the quality of evidence (GRADE) in a consensus discussion.

Endothermal ablation compared with surgery (PICO 1)

Health related quality of life (Appendix 4.1.1)

Three RCTs included in the NICE guidance assessed health-related quality of life (HRQoL). One used the score of the Aberdeen Varicose Vein Symptoms Severity Score Questionnaire (AVVQ) and two the Chronic Venous Insufficiency Questionnaire CIVIQ-2 at 1-12 weeks, one year and two years. Three additional RCTs were published later than Oct 7th, 2012. One reported the CIVIQ and the EuroQoL-5D scores (EQ-5D) at one year, and another reported AVVQ scores and the Short Form 36 (SF-36). A third RCT reported only the AVVQ scores. All observed intergroup differences for HRQoL were small and non-significant whereas intragroup differences for, e.g., the disease-specific instrument AVVQ were significant in both treatment groups (AVVQ range 0 – 100, the lower the better) from18.7 to 4.0 and from 19.3 to 4.6 from baseline to three years after endothermal ablation and surgery, respectively, in one RCT.

Conclusion: There may be little or no difference in HRQoL one year after endothermal ablation compared with conventional surgery. Low quality of evidence (GRADE ⊕⊕◯◯).

Symptomatic recurrence

There was no published study that reported data on symptomatic recurrence.

Presence of reflux (Appendix 4.1.2)

The NICE guidance included eight RCTs that reported saphenous truncal reflux after 0-12 weeks. Six of them also reported return of reflux after one to three years: 7.0% after endothermal ablation (n=513) and 5.6% after surgery (n= 342) at one to three years. An additional four RCTs were published after the NICE guidance. None of the latter RCTs reported any significant differences between the study groups.

Conclusion: There may be little or no difference in the presence of reflux at short-term (one to 12 weeks) and long-term (mainly data after six to 12 months) follow-up after endothermal ablation compared with surgery. Low quality of evidence (GRADE ⊕⊕◯◯).

Time to return to work (Appendix 4.1.3)

Two RCTs included in the NICE guidance compared RFA with surgery and two compared EVLA with surgery. The results suggested a shorter time to return to work for patients treated with RFA compared with surgery (4.7 – 6.5 versus 12.4 – 15.6 days) but this was not observed for EVLA compared with surgery (4.4 – 7.0 versus 4.2 – 7.6 days). One RCT published after October 17, 2012, compared EVLA with surgery and reported that more patients returned early to work after EVLA (97,6% versus 89% at work at two weeks, $p< 0.05$).

Conclusion: Time to return to work may be slightly shorter after endothermal ablation compared with surgery. Low quality of evidence (GRADE ⊕⊕◯◯).

Postoperative pain (Appendix 4.1.4)

Post-operative pain was reported in eight RCTs included in the NICE guidance. No intergroup differences were observed. One RCT was published later. It compared EVLA with surgery, and reported slightly more postoperative pain (VAS, 0 – 100, 100 worst) seven days after EVLA than after surgery (VAS 31 versus 18; $p<0.05$). There was no difference at two weeks.

Conclusion: There may be little or no difference in postoperative pain after endothermal ablation compared with surgery. Low quality of evidence (GRADE ⊕⊕◯◯).

Clinical status (Appendix 4.1.5)
One RCT included in the NICE guidance reported Venous Clinical Severity Score (VCSS, range 0 – 33, 33 worst) up to 50 days and at three years with no significant differences. Two RCTs published later reported VCSS scores. Both of them reported exceptionally low baseline scores (2.4 – 2.8) indicating that a large proportion of the study patients were treated for cosmetic reasons. The VCSS score was 0.3 at three years in both groups. None of the studies showed any significant differences between treatments at three and five years.
Conclusion: It is uncertain whether there is any difference in the VCSS during long-term follow-up after endothermal ablation compared with conventional surgery.
Very low quality of evidence (GRADE ⊕◯◯◯).

Ultrasound guided foam sclerotherapy (UGFS) compared with surgery (PICO 2)

Health related quality of life (Appendix 4.2.1)
Two RCTs that reported the effects on health-related quality of life were included in the NICE guidance. One used the SF-36-Physical and the other the EQ-5D questionnaire. Another two RCTs were published later using different instruments (CIVIQ, EQ-5D, SF-36-Physical, SF-Mental and AVVQ). For the generic instruments (EQ-5D, SF-36), intra- and intergroup changes were small and not significant. For the disease-specific instrument AVVQ (range 0 – 100, the lower the better), intragroup changes were significant (18.4 – 4.8 and 19.3 - 4.0 from baseline to three years after UGFS and surgery respectively) while intergroup differences were not significant. In summary, there were no significant intergroup differences at one or three years of follow-up in any of the studies.
Conclusion: There is probably little or no difference in HRQoL one or three years after UGFS compared with surgery. Moderate quality of evidence (GRADE ⊕⊕⊕◯).

Symptomatic recurrence
There was no published study that reported data on symptomatic recurrence.

Presence of reflux (Appendix 4.2.2)
The NICE guidance included four RCTs that studied the presence of truncal reflux after intervention showing a higher frequency of reflux after UGFS compared with surgery (28.3% vs 15.0%). Another two RCTs were published later. The latter two studies showed a higher frequency of reflux after UGFS (26.4 % to 28.3% at one and three years) compared with surgery (6.5 % to 15% at one and three years).
Conclusion: Truncal reflux is probably more frequent one and three years after UGFS compared with surgery. Moderate quality of evidence (GRADE ⊕⊕⊕◯).

Time to return to work (Appendix 4.2.3)
Time to return to work was only reported in one RCT. It was included in the NICE guidance. No significant differences were found between UGFS and surgery (2.9 and 4.3 days respectively).
Conclusion: It is uncertain whether there is any difference in time to return to work after UGFS compared with surgery. Very low quality of evidence (GRADE ⊕◯◯◯).

Postoperative pain (Appendix 4.2.4)
Postoperative pain was studied in two RCTs, both of which were included in the NICE guidance. One of them used a visual analogue scale (VAS) and the other reported the percentage of patients with postoperative pain. There was little or no difference in the severity of postoperative pain (1.6 and 2.3 for UGFS and surgery respectively), according to the VAS scale (range 0 – 10, 10 worst), and less patients had postoperative pain after UGFS compared with surgery (25% versus 80% respectively).
Conclusion: There may be slightly less postoperative pain after UGFS compared with surgery.
Low quality of evidence (GRADE ⊕⊕◯◯).

Clinical severity (Appendix 4.2.5)
The venous clinical severity score was reported in one RCT included in the NICE guidance. The decrease in VCSS at two years was -1.8 and -1.5 after UGFS and surgery respectively (n.s. intergroup difference). Another RCT was published later. There was no intergroup difference in VCSS from baseline to three years (2.7 – 0.2 and 2.8 – 0.3 after UGFS and surgery respectively).
Conclusion: There may be little or no difference in VCSS at two and three years after UGFS compared with surgery.
Low quality of evidence (GRADE ⊕⊕◯◯).

Foam sclerotherapy compared with endothermal ablation (PICO 3)

Health related quality of life (Appendix 4.3.1)
Two RCTs that reported the effects on HRQoL were included in the NICE guidance. One used the SF-36-Physical and the other the AVVQ questionnaire. An additional three RCTs were published later using different questionnaires (CIVIQ, EQ-5D, SF-36-Physical, and AVVQ). For the generic instruments (EQ-5D, SF-36), intragroup changes were small and intergroup differences were small and not significant. For the disease-specific instrument AVVQ (range 0 – 100, the lower the better), the median decrease in AVVQ in the NICE report was 9 and 12 after UGFS and endothermal ablation respectively. In summary, there were no significant intergroup differences at one or three years of follow-up in any of the studies.
Conclusion: There is probably little or no difference in HRQoL one year after UGFS compared with endothermal ablation. Moderate quality of evidence (GRADE ⊕⊕⊕◯).

Symptomatic recurrence
There was no published study that reported data on symptomatic recurrence.

Presence of reflux (Appendix 4.3.2)
Presence of reflux was reported in one RCT in the SR and in three RCTs published later. The rate of truncal reflux ranged from 16.3% to 32.6% at follow-up one to three years after UGFS compared with 4.5% to 11.5% after endothermal ablation.
Conclusion: Ultrasound guided foam sclerotherapy is probably associated with a higher rate of truncal reflux at one year compared with endothermal ablation.
Moderate quality of evidence (GRADE ⊕⊕⊕◯).

Time to return to work (Appendix 4.3.3)
Only one RCT reported the time to return to work. It was included in the NICE guidance. There was no difference between patients treated with UGFS and endothermal ablation.
Conclusion: It is uncertain whether there is any difference in time to return to work after UGFS compared with endothermal ablation. Very low quality of evidence (GRADE⊕◯◯◯).

Postoperative pain (Appendix 4.3.4)
One RCT reported on postoperative pain. It was included in the NICE guidance. There was no significant difference in pain (VAS scale 0 – 10, 10 worst) after 10 days between patients treated with UGFS compared with endothermal ablation (VAS 1.6 after UGFS and 2.6 and 1.2 after EVLA and RFA respectively).
Conclusion: There may be little or no difference in post-operative pain after UGFS compared with endothermal ablation. Low quality of evidence (GRADE ⊕⊕◯◯).

Clinical severity (Appendix 4.3.5)
Venous clinical severity score was reported in one RCT that was included in the NICE guidance. The change in VCSS from baseline to three months was -4 after UGFS and endothermal ablation. Another two RCTs were published later. There were no differences between study groups at follow-up up to three years (from baseline to three years: 2.7 to 0.2 after UGFS and from 2.7 and 3.0 to 0.2 and 0.4 after EVLA and RFA respectively).
Conclusion: There is probably little or no difference in VCSS during follow-up until three years after UGFS compared with endothermal ablation. Moderate quality of evidence (GRADE⊕⊕⊕◯).

Complications (Appendix 5 a-c)
Complications after endovenous interventions or surgery mainly include thromboembolic complications, wound infection, nerve injuries and skin discoloration. Phlebitis was not infrequent after endothermal ablation and UGFS (14.1 % and 9.7 %, respectively). Pulmonary embolism (PE) is reported to occur in low frequencies after endothermal ablation and UGFS (0.06 % and 0.4 %, respectively). The incidence of postoperative deep venous thrombosis (DVT) in the RCTs in the NICE guidance was 0.2%, 1.5% and 0.4% in the endothermal ablation, UGFS and surgery groups respectively. In the largest case series (>4000 patients), the frequency of DVT was 2.1% after endothermal ablation. In a prospective study with repeated ultrasound examinations after varicose vein surgery, there were 20 (5.3%) postoperative DVT but no PE in 377 patients (van Rij et al, 2004).
No surgical/puncture site infections were reported after endothermal ablation or UGFS, but in 7.5 % after surgery. Various minor cutaneous nerve injuries were moderately common after endothermal ablation (5.2%) and surgery (8.1%), but uncommon in patients treated with UGFS (0.7 %).
The occurrence of skin discoloration was 3.1 %, 16.9 % and 7.0 % after endothermal ablation, UGFS and surgery, respectively.

9. Ethical consequences

Ethical consequences

Short- and medium-term data suggest that the use of endovenous techniques may be less costly, provided that indications for intervention are unchanged, and with similar short- and medium-term results regarding HRQoL as surgery. Long-term results of endovenous techniques are not known. The critical outcome symptomatic recurrence is not reported in any study.There are ethical aspects on introducing techniques into routine clinical practice when long-term results and cost-effectiveness are poorly known. Endovenous techniques reduce the overall need for operation theatres releasing operating theatre resources. Since long term outcomes (beyond three years) are largely unknown, there may be a risk of late recurrences that might become more frequent than for standard surgical treatment. Endovenous techniques may increase the communication between the patient and the surgeon since it is conducted in local anaesthesia. The patient´s autonomy is less affected for interventions that do not require general anaesthesia. However, surgery can also be performed using local anaesthesia as performed in several studies included in this analysis.

Patients should be involved in the decision-making regarding the choice of treatment modality, suggesting that we should offer more than one option. Since the short and medium term results appear to be similar the patients wish ought to be respected as far as possible. This may suggest that caregivers should be able to offer surgery and at least one alternative endovenous method.

10. Organisation

When can endovenous interventions on varicose veins be put into practise?

After training of personnel in ultrasound examination and endovenous treatment. Approximately 3x8 hours of training for surgeons and 3x8 hours for assisting personnel are estimated for being able to perform the ablation. To be familiar with venous ultrasound scanning for diagnostic purposes considerably more training is necessary, probably around 120 hours and including attendance at duplex courses.

Endovenous interventions used in hospitals in Region Västra Götaland of Sweden

Radiofrequency ablation is currently in use in South Älvsborg Hospital (SÄS) and in North Älvsborg hospital (NÄL), but not in Skaraborg hospital or in Sahlgrenska University Hospital.

The consequences of endovenous interventions for personnel

All involved personnel need to be trained to use the equipment needed for these interventions. Especially the interventionist/surgeon need to be well trained to perform duplex scanning. Since these methods of intervention can be performed in treatment rooms with a limited need of advanced equipment in outpatient settings more resources will be available for other surgical procedures in regular operating theatres (c.f. appendix 7). Endovenous interventions do not require an anaesthesiologist or an anaesthetic nurse. Thus, also the need for specialized staff will be reduced.

The consequences for other clinics or supporting functions at the hospitals and in the whole Region Västra Götaland of Sweden

A substantial number of interventionists/surgeons/vascular surgeons have to receive appropriate training in endovenous techniques and in handling duplex ultrasound. Furthermore, a number of duplex machines have to be purchased. Diagnostic duplex ultrasound must be available but can be organized in different ways depending on available resources in each hospital. If more duplex ultrasound examinations are performed by vascular surgeons, the demand for such examinations in clinical physiology departments will probably decrease.

It is important to understand that endovenous methods cannot deal with all kinds of varicose vein patients and that there will still be a need for surgical interventions, especially for the more severe cases and for cases with recurrence. Therefore, the endovenous techniques will serve as a complement to open surgery. Once available, hybrid procedures are likely to become more common especially for patients with varicose vein recurrence where a combination of open surgery and most often UGFS may become a very effective treatment combination. To combine surgery with endothermal ablation is a less effective alternative, except for local stab excisions of varicose clusters that are usually combined with the primary endothermal treatment. Currently, 31% and approximately 25% of invasive interventions for symptomatic varicose veins in UK and Region Västra Götaland, respectively, are performed by endothermal ablation. In a study from UK, 60% of primary truncal reflux patients were suitable for EVLA (Sherif et al., 2006). If we assume that 60-70% of varicose vein patients have primary truncal reflux, approximately 40% of all varicose vein patients could thus be treated by endothermal ablation.

The estimation of hours saved in the operating theatres

The estimation of annual hours saved in the operating theatres within Region Västra Götaland due to an increase of endovenous treatments is based on the assumption that each patient that could be treated with endovenous treatment instead of conventional surgery will release 1.5 hours in the operating theatre. Total annual patients treated for varicose veins in Region Västra Götaland is 1300, whereof 25% are treated with endovenous techniques. An assumption is made that varicose veins interventions are performed during 40 weeks per year. Based on the assumption that all 1300 patients are treated during the year, there is a capacity to treat 975 patients annually with conventional surgery and 325 patients annually with endovenous treatments. The second scenario estimation, based on 40% endovenous treatments, would result in a reduction of 195 patients which were previously treated with conventional surgery and thereby release 293 hours in the operating theatre. The third scenario, based on 70% endovenous treatment, would reduce 585 conventional surgeries resulting in 878 released hours in the operating theatres. The capacity of conventional surgery is 4 legs per day, 1.5 hours for each surgery, by this the capacity of each operating theatre is 30 hours per week and 1200 hours per year under the assumption that varicose veins interventions are performed during 40 weeks per year. With the second scenario, one-fourth of an operating theatre will annually be released and with the third scenario, three quarters of an operating theatre will annually be released compared to present strategy.

	ANNUAL PATIENTS TO BE TREATED WITH SURGERY	ANNUAL HOURS WITH SURGERY	ANNUAL PATIENTS TO BE TREATED RFA/EVLA	ANNUAL HOURS WITH RFA/EVLA	ANNUAL HOURS RELEASED IN OPERATING THEATRES	ANNUAL OPERATING THEATRES RELEASED
PRESENT STRATEGY (75/25)	975	900	325	150		
SCENARIO 1 (70/30)	910	840	390	180	**98**	
SCENARIO 2 (60/40)	780	720	520	240	**293**	1/4
SCENARIO 3 (30/70)	390	360	910	420	**878**	3/4

Medical societies or health authorities that recommend endovenous interventions on varicose veins

In the NICE guidance for UK, it is recommended that patients with symptomatic varicose veins should be referred to a vascular specialist for clinical and ultrasound examination. For treatment, endothermal ablation is recommended as first choice, if suitable, for confirmed varicose veins and truncal reflux. If endothermal ablation is unsuitable, UGFS is recommended. If UGFS is unsuitable, surgery is recommended.
In the US, endothermal ablation is recommended by the American Venous Forum and the Society of Vascular Surgery.

11.Economic aspects

Present costs of currently used technology

Cost per patient for conventional surgery is estimated to 15 000 SEK for patients within the Region Västra Götaland, excluding patients who had surgery at Sahlgrenska University hospital, were the cost per patient is estimated to 44 000 SEK. Cost per patients includes health care personnel, material cost, theatre costs and costs of care after day surgery, cost of infections and overhead costs. Cost per patient estimated for patients who had surgery at Sahlgrenska University hospital also includes inpatient care after surgery (in average 1.5 days). Calculation is based on ICD-code I83 and the surgery code PHD 10, 12 and 99. Risk of infection is based on the study by Hinchcliffe et al 2006, showing that 1 per 32 patients had an infection after the surgery. Cost of infections after surgery is estimated to cause one visit to the hospital with an average cost per visit of 4000 SEK. The total annual costs is based on the approximately 1 300 patients in Region Västra Götaland that underwent invasive interventions during 2014. Currently used treatment strategy constitutes of approximately 75% conventional surgery and 25% with endothermal ablation. By this, the annual cost is estimated to 19 million SEK. The total cost consists of 800.000 SEK for patients who had surgery at Sahlgrenska University hospital and 18.2 million SEK for patients who had surgery within the rest of Region Västra Götaland.

Expected costs of treatment with new technologies?

Cost per patient with treatment with RFA/EVLA is estimated to 10 000 SEK including health care personnel, material cost, outpatient care costs and laser and radiofrequency equipment and overhead costs. Calculation is based on ICD-code I83 and the treatment codes PHT 10, 12 and 99 as well as PHV 10, 12 and 99.

Cost per patient with UGFS was not possible to estimate within the settings of the Region Västra Götaland due to lack of information as a result of too few procedures. However, previous literature have found that UGFS is less costly for the health care budget compared to surgery.

Total change of cost

The total annual change in cost with surgery compared to RFA/EVLA is illustrated by three scenarios. The first scenario was based on 70% of the patients were treated with surgery while 30% with RFA/EVLA. The second scenario was based on 60% treatments with surgery and 40% with RFA/EVLA. The third illustrates a scenario based on 30% treatments with surgery and 70% with RFA/EVLA. The total change of cost will be partly dependent on the need for repeated interventions for recurrent truncal reflux or reflux in another saphenous vein trunk. Long-term data for these events are not available for endothermal ablation.

Table 1. The total annual cost is based on the cost estimation for patients within Region Västra Götaland (excluding Sahlgrenska University hospital).

	ANNUAL COST WITH SURGERY	ANNUAL COST WITH RFA/EVLA	TOTAL COST IN REGION VÄSTRA GÖTALAND
PRESENT COSTS	14 967 400 kr	3 250 000 kr	**18 217 400 kr**
SCENARIO 1	13 901 000 kr	3 900 000 kr	**17 801 000 kr**
SCENARIO 2	11 915 200 kr	5 200 000 kr	**17 115 200 kr**
SCENARIO 3	5 957 600 kr	9 100 000 kr	**15 057 600 kr**

The scenario estimations for procedures within the Sahlgrenska University hospital shows that the cost savings are greater with higher frequency of RFA/EVLA as a result of the differences in cost per patient.

In conclusion, annual total cost for surgery is greater than the total annual total cost for RFA/EVLA, resulting in the more procedures using RFA/EVLA the less will the total annual cost be for treating symptomatic varicose veins in the Region Västra Götaland. Total annual cost is presented in a health care perspective, i.e. only direct cost within the health care is included in the cost analysis. However would the total annual cost be presented with a societal perspective, including loss of production, then the annual total cost be even greater for surgery compared to EVLA/RFA due to previous studies showing that return to work is earlier with endovenous treatments compared to surgery. On the other hand, long-term data for need of repeated intervention after endothermal ablation is not available, thereby the cost of retreatments is not included in the estimation. This might increase the cost per patient to some extent. The scenario estimation was not possible to estimate for UGFS due to lack of information. Though, previous cost analysis have shown that UGFS is less costly compared to surgery. By this, assumption can be made that the scenario estimation would have a similar trend for UGFS as for RFA/EVLA.

Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

Due to new technology is estimated to be less costly, present budget will not be affected by any excess costs due to the new technology.

Are there any available analyses of health economics?

The Health Technology Assessment by Carroll et al, 2013, included four economic analyses. Two analyses compared RFA with surgery and both had a short-term perspective with less than 40 days and based the resource utilisation from clinical trials, both from the UK (Subramonia and Lees, 2010, and Adi et al., 2004). Both studies showed RFA to be more costly than surgery. Adi et al., 2004, estimated QALY from differences in mean pain VAS scores, giving an incremental cost-effectiveness ratio (ICER) for RFA compared with surgery of £23750 per gained QALY. The study compared EVLA with cryostripping (Disselhoff et al., 2009) showed EVLA to be marginally more effective and more expensive than cryostripping. The study is of poor quality and has some incorrect calculations which were recalculated by Carroll et al., 2013. The differences in costs and QALYs were small in comparison to their uncertainties so treatment alternatives are similar in terms of both costs and QALYs. The modelling study compared the endovenous treatments (UGFS, EVLA and

RFA) with surgery over a 5-year time horizon (Gohel et al., 2010) showed similar costs and benefits for all treatment alternatives. Sensitivity analysis was undertaken, however, some key assumptions were not tested in sensitivity analysis, i.e. same recurrence rate for all treatments, utility value for clinical failed treatments. The result from the economic model completed by Carroll et al. themselves showed that the difference in QALYs between the treatment alternatives were negligible. The differences in costs are, however, more significant although there are some notable uncertainties. By this, with minor differences in QALYs the ICER is most driven by costs. The estimates from the model was that UGFS is less costly than surgery and is marginally more effective. EVLA and RFA both cost more than surgery and with a minor difference in QALYs they cannot be considered cost-effective. The model also included time to work or usual activities, which showed to be earlier for UGFS, RFA and EVLA compared to stripping surgery. By this, UGFS is the most cost-effective option in both an NHS and a societal perspective.

The NICE guidance "Varicose veins in the legs", 2013, included the economic model by Gohel et al., 2010, as well as a model completed by the NCGC. The model completed by NCGC showed that UGFS was cost-effective compared to surgery, however, neither UGFS nor surgery were cost-effective compared to endothermal treatment. This result was not consistent with the result by the Gohel analysis, which is considered to have some potentially serious limitation, mentioned above. According to the Gohel analysis endothermal treatment was considered to be more cost-effective compared to UGFS, however, not compared to day surgery.

Lattimer et al., 2013b, compared different costing methods in the UK settings for three endovenous treatments in varicose veins; LA, tumescent foam and UGFS. The source of costing data contained both top-down (micro-costing) and bottom-up approaches and the results showed significant differences in the costing methods and had the conclusion that several costing approached is necessary within a cost-effectiveness analysis.

Kuhlmann et al 2013, assessed a budget impact model comparing a scenarios with full use of ClosureFast (radiofrequency ablation) versus no use of ClosureFast. The Markov model estimated that an introduction of ClosureFast would save €19.1 million in the German Statutory Health Insurance. Sensitivity analysis were completed to address the uncertainties in the input parameters and showed that the model is highly sensitive to variation in prices of the interventional treatment.

In conclusion, the economic analyses all provided similar result in that the difference in costs and benefits between the treatment alternatives are small and sensitive to different assumptions. The majority of the economic analyses was undertaken from a UK NHS perspective. With minor differences in QALYs the between the different treatment alternatives the ICER is most influenced by the cost of the various alternatives. The cost-effectiveness of surgery compared to the different endovenous treatments may vary with local cost, and is likely to be uncertain. By this, it is not possible to translate the results from the UK studies into the Swedish settings due to differences in costs in local health care systems.

12. Unanswered questions

Important gaps in scientific knowledge

As previously stated, the long-term durability (beyond three years) of the results of endovenous treatments is poorly known. Thus, there may be a risk of accumulated need for re-treatments after five to 10 years. For technical reasons, endothermal ablation of truncal incompetence in the greater saphenous vein always results in a remaining incompetent short proximal segment (stump) of the saphenous vein, and an unknown fraction of these patients may develop incompetent anterior accessory saphenous veins during late follow-up. There are data indicating more groin recurrence due to stumps following endothermal ablations after five years, which may be a risk factor for later symptomatic recurrence requiring repeat interventions (Nelzén, 2014). We do not know the magnitude of this problem or whether it will be greater than the present need for redo surgery following primary surgery.

Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes. There is a need for several studies, but we have not yet planned any study.
A study to identify the early need for retreatments because of insufficient occlusion of the treated truncal vein using a one month duplex control after endovenous treatments would be of interest.
A study regarding the best treatment of groin recurrence, open redo groin surgery, UGFS or a hybrid approach (Surgery + UGFS) would also be of interest.
If endovenous treatments are widely introduced, prospective registration of performed retreatments following the initial procedure would be of interest.

Ongoing research

A search in Clinicaltrials.gov (2015-02-02) using the search terms
(Varicose vein* OR Varices OR Varix OR Varicosities* OR Saphenous* OR Venous ulcer* OR Varicose Ulcer OR Leg ulcer* OR Venous insufficiency) AND (Radiofrequency OR RFA OR RFITT OR Sclerotherapy OR UGFS OR ultrasound-guided OR Ablation* OR Catheter* OR Endovenous* OR EVL OR EVLA OR EVLO OR EVLT OR Thermal* OR Endothermal* OR Laser* OR Endovenous*) identified 67 trials. Only three were relevant for our question:

1. Prospective Randomized Trial Comparing the New Endovenous Procedures Versus Conventional Surgery for Varicose Veins Due to Great Saphenous Vein Incompetence (RAFPELS). RCT comparing EVLA, RFA, UGFS and CS. The study started 2008 and was finalised in January 2014 with 540 patients enrolled. Results not yet published. The study was performed in Västerås, Sweden.
2. Long-term Ultrasound Guided Foam Sclerotherapy Versus Classical Surgical Stripping Study. Prospective comparative registry study between UGFS and CS. The study started November 2014 and the estimated primary completion data is October 2015. Estimated enrolment 460 patients. Long term follow-up, 6-10 years, is planned. Primary outcome long term HRQoL. Secondary outcomes clinical and technical recurrence. The study is performed in Maastricht, The Netherlands.

3. Prospective Multicentric Trial Between Radiofrequency Ablation With VNUS Closure Fast ® and Endovenous Ablation With 1470 nm Diode Laser and Tulip Fiber ® for Treatment of Primary Venous Insufficiency. (VNUS vs TULIP). Prospective multicentre RCT comparing EVLA (1470nm laser with Thulip Fiber® with RF (VNUS Closure Fast®). Primary outcome measures: Closure of the GSV at 12 months assessed by duplex ultrasound. Secondary outcomes pain scores, patient satisfaction and incapacity to work at various time intervals. The study started in January 2014 and the estimated study completion date is June 2016. Primary outcome will be assessed in December 2015. The study originates from the University Hospital in Ghent, Belgium.

Appendix 1: Search strategy, study selection and references

Question at issue:
Are endovenous techniques better than open surgery for adult patients with symptomatic lower limb varicose veins with truncal reflux regarding health related quality of life, symptomatic recurrences, time to return to work and postoperative complications?

PICO 1

P	Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb
I	Endothermal ablation
C	Conventional surgery
O	<u>Critical</u> Health related quality of life (measured with validated scales) Symptomatic recurrence <u>Important but not critical</u> Presence of reflux Time to return to work Postoperative pain Clinical status

PICO 2

P	Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb
I	Foam sclerotherapy
C	Conventional surgery
O	<u>Critical</u> Health related quality of life (measured with validated scales) Symptomatic recurrence <u>Important but not critical</u> Presence of reflux Time to return to work Postoperative pain Clinical status

PICO 3

P	Adult patients with symptomatic varicose veins and duplex verified truncal reflux of the lower limb
I	Foam sclerotherapy
C	Endothermal ablation
O	Critical Health related quality of life (measured with validated scales) Symptomatic recurrence Important but not critical Presence of reflux Time to return to work Postoperative pain Clinical status

Eligibility criteria

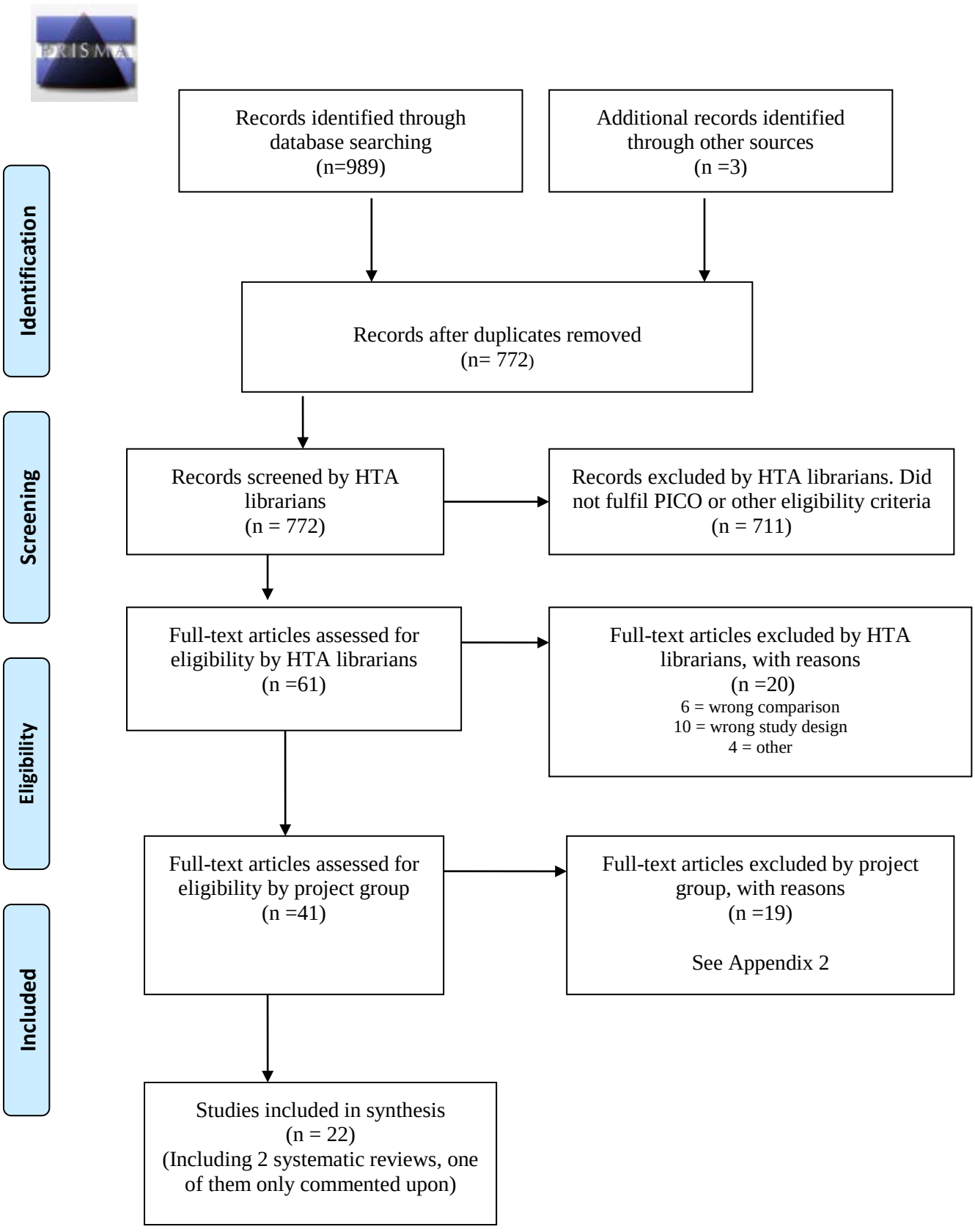
Study design:
Systematic reviews
Randomized controlled trials
Case series ≥ 350 limbs (for outcome: risks/complications)

Language:
English, Swedish, Norwegian, Danish

Publication date:
Search date from 2012-10-17

Comment:
This report is based on the NICE guidelines ”Varicose veins in the legs” (July 2013) with last literature search date 2012-10-17

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2014-06-27
No of results: 246

Search	Query	Items found
#21	**Search #14 NOT #15 Filters: Publication date from 2012/10/01; Danish; English; Norwegian; Swedish**	**246**
#16	Search #14 NOT #15	4324
#15	Search ((child[mh]) NOT (child[mh] AND adult[mh]))	953852
#14	Search #12 NOT #13	4443
#13	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3900803
#12	Search #10 NOt #11	4511
#11	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1330402
#10	Search #3 AND #9	4845
#9	Search #4 OR #5 OR #6 OR #8	105777
#8	Search Radiofrequency obliteration[tiab] OR RFO[tiab] OR Radiofrequency ablation[tiab] OR Radio frequency ablation[tw] OR Radio-frequency ablation[tiab] OR RFA[tiab] OR RFITT[tiab] OR Bipolar radiofrequency induced thermotherapy[tiab]	10435
#6	Search Endovenous laser*[tiab] OR Laser therapy[mh] OR Laser ablation[tiab]	51434
#5	Search Ablation techniques[mh] OR Catheter ablation[tiab] OR Catheter ablation[mh] OR Endovenous ablation[tiab] OR Endovenous thermal ablation[tiab] OR EVL[tiab] OR EVLA[tiab] OR EVLO[tiab] OR EVLT[tiab] OR Thermal ablation[tiab] OR Endothermal ablation[tiab]	90347
#4	Search Sclerotherapy[mh] OR (Sclerotherap*[tiab] AND Foam[tiab]) OR Foam sclero*[tiab] OR ugfs[tiab] OR ultrasound-guided foam sclerotherapy[tiab] OR microfoam sclerotherapy[tiab] OR Sclerosing solutions[mh]	7671
#3	Search #1 OR #2	54068
#2	Search Venous ulcer*[tiab] OR Venous disease*[tiab] OR Venous leg ulcer*[tiab] OR Varicose Ulcer[mh] OR varicose leg ulcer*[tiab] OR Venous insufficiency[mh] OR Venous insufficiency[tiab]	12290
#1	Search Varicose veins[mh] OR Varicose vein*[tiab] OR Varices[tiab] OR Varix[tiab] OR Varicosis[tiab] OR Varicosit*[tiab] OR Saphenous vein[mh] OR Saphen*[tiab]	48094

Database: EMBASE (OVID SP)
Date: 2014-06-27
No of results: 565

#	Searches	Results
1	exp varicosis/	41045
2	saphenous vein/	11289
3	(varicose vein$ or varices or varix or varicosis or varicosit$ or saphen$).ti,ab.	41877
4	leg ulcer/	11180
5	vein insufficiency/ or chronic vein insufficiency/	7660
6	(venous ulcer$ or venous disease$ or venous leg ulcer$ or varicose leg ulcer$ or varicose ulcer$ or venous insufficiency).ti,ab.	10466

7	1 or 2 or 3 or 4 or 5 or 6	82014
8	exp sclerotherapy/	9776
9	exp sclerosing agent/	10317
10	(foam adj5 sclero$).ti,ab.	687
11	(ugfs or ultrasound-guided foam sclerotherapy or microfoam sclerotherapy).ti,ab.	157
12	8 or 9 or 10 or 11	17126
13	ablation therapy/	6863
14	catheter ablation/	21394
15	(catheter ablation or endovenous ablation or endovenous thermal ablation or EVL or EVLA or EVLO or EVLT or thermal ablation or endothermal ablation).ti,ab.	13744
16	13 or 14 or 15	30598
17	(endovenous laser$ or laser therapy or laser ablation).ti,ab.	12146
18	radiofrequency ablation/	17137
19	(radiofrequency obliteration or RFO or radiofrequency ablation or radio frequency ablation or radio-frequency ablation or RFA or RFITT or bipolar radiofrequency induced thermotherapy).ti,ab.	15499
20	18 or 19	23215
21	12 or 16 or 17 or 20	74306
22	7 and 21	9627
23	(animal not (animal and human)).sh.	1181912
24	22 not 23	9611
25	(child not (child and adult)).sh.	814887
26	24 not 25	9360
27	(rat or rats or mice or mouse or child$ or pediatr$).ti.	1903899
28	26 not 27	9236
29	**limit 28 to (embase and (danish or english or norwegian or swedish) and yr="2012 - Current" and (article or conference paper or "review"))**	**565**

Database: The Cochrane Library
Date: 2014-06-27
No of results: 177*
Cochrane reviews
Other reviews
Technology assessments
Trials: 83
Economic evaluations

*This is the combined results of two searches. #3 below was used for Cochrane reviews, Other reviews, Technology assessments and Economic evaluations, a total of 94 references. #5 below was used for Clinical trials, a total of 83 references.

Search Name:		
ID	Search	Hits
#1	(Varicose next vein*) or Varices or Varix or Varicosis or Varicosit* or Saphen*:ti,ab,kw (Word variations have been searched)	3050
#2	(Venous next ulcer*) or (Venous next disease*) or (Venous next leg next ulcer*) or (Varicose near/3 ulcer*) or (Venous next insufficiency):ti,ab,kw (Word variations have been searched)	1630
#3	**#1 or #2**	4458

#4	Radiofrequency or radio-frequency or (radio next frequency) or RFA or RFITT or laser or ablation or thermal or EVL or EVLA or EVLO or EVLT or endothermal or endovenous or sclero* or UGFS:ti,ab,kw (Word variations have been searched)	20107
#5	**#3 and #4 Publication Year from 2012 to 2014**	100

The web-sites of **SBU, Kunnskapssenteret**, **Sundhedsstyrelsen** and **CRD** were visited 2014-06-27. One relevant reference relevant to the question at issue was found in CRD "Lattimer CR et al. Cost-effectiveness in varicose vein treatment".

Reference lists
A comprehensive review of reference lists brought 3 new records

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Reference lists

Included studies:

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Kane K, Fisher T, Bennett M, Shutze W Jr, Hicks T, Grimsley B, et al. The Incidence and Outcome of EHIT after Endovenous Laser Ablation. Ann Vasc Surg. 2014 Jun 6. pii: S0890-5096(14)00305-7. doi: 10.1016/j.avsg.2014.05.005. [Epub ahead of print]

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Appendix 2 – Treatment of varicose veins. Included studies – design and patient characteristics.
Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life).

Author, Year, Country	**Study design**	**Time of follow-up**	**Study groups**	**Patients/Limbs (n/n)**	**Mean age (years) (range or sd)**	**Men (%)**	**Outcome variable**
NICE Guidance 2013,UK		Various in different RCTs	RFA EVLA UGFS CS	Various in different RCTs	Various in different RCTs	Various in different RCTs	Technical success, Recurrent varicose veins, Pain, Quality of Life
Carroll 2013 NHS, UK	HTA-report of 34 RCTs	Various in different RCTs	RFA EVLA UGFS CS	Various in different RCTs	Various in different RCTs	Various in different RCTs	Technical success, Recurrent varicose veins, Pain,Quality of Life
Biemans 2013 Netherlands & Belgium	RCT	1 year	UGFS EVLA CS	78 77 68	49 (15) 56 (13) 52 (16)	31 33 32	Anatomic success CEAP class, HRQoL
Flessenkamper 2013, Germany	RCT	6 months	EVLA CS	142/- 159/-	49	29	Clinical recurrence Ultrasound recurrence
Lattimer 2013a UK	RCT	15 months	EVLA UGFS	44/44 46/46	48 (23-78)	42	GSV occlusion Venous reflux
Rasmussen 2013a (J Vasc Surg) Denmark	RCT	6 months 5 years	EVLA CS	62/69 59/68	53 (26-79) 54 (22-78)	34 27	Open reflux Recurrent varicose veins Reoperations, Quality of Life
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis),Denmark	RCT	3 years	UGFS EVLA RFA CS	125/145 125/144 125/148 125/143	51 (18-75) 52 (18-74) 51 (23-77) 50 (19-72)	24 28 30 23	Technical success Recurrent varicose veins Reoperations Quality of Life
Roopram 2013 Netherlands	RCT	6 weeks	EVLA CS	118/- 57/-	52 (21-79) 51 (19-73)	27 46	Vascular incompetence /recanalization, Quality of life, Cosmetic result, Operating time, Pain, No of days to normal activity of life
Samuel 2013 a UK	RCT	1 year	EVLA CS	53/53 53/53	48 (12) 48 (13)	36 26	Technical success, Pain, Time return to work, Quality of life
Asciutto 2012 Sweden	Case series	Up to 4 years	UGFS	337/357	59 (18-95)	39	Complications

Appendix 2 – Treatment of varicose veins. Included studies – design and patient characteristics.
Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life).

Author, Year, Country	**Study design**	**Time of follow-up**	**Study groups**	**Patients/Limbs (n/n)**	**Mean age (years) (range or sd)**	**Men (%)**	**Outcome variable**
Braithwaite 2013 7 European countries	Case series	0.5 – 1 year	RFA	462/672	51 (13)	34	Complications
Chi 2014 USA	Case series	1 week	EVLA	353/360	58 (14)	30	Complications
Harlander-Locke 2013	Case series	24 -72 hours	RFA	735/916	57(12)	27	Complications
Kane 2014 USA	Case sries	Not reported	EVLA	418/528	55 (15)	36	Thromboembolic complications
Moul 2014 USA	Case series	11.4 months (mean)	EVLA	-/1171	56 (22-88)	30	Complications
Newman 2014 UK	Case series	1 year	RFA	520/655	54 (14)	40	Complications
Rhee 2013 USA	Case series	1,7 days (1-8)	EVLA RFA	-/234 -/285	Not reported	Not reported	Thrombosis
Sadek 2103 USA	Case series	16 weeks (mean)	EVLA RFA	-/4223	51(14)	Not reported	Thrombosis Complications
Sufian 2013	Case series	2 – 3 days	RFA	-/6707	Not reported	Not reported	Thrombosis
Sufian 2014	Case series	2 – 3 days	EVLA	-/2168	Not reported	Not reported	Thrombosis
Tolva 2013 Italy	Case series	Up to 1 year	-/407	55 (19 – 84)	15	Not reported	Complications
Zuniga 2012 USA	Case series	1 year	RFA	581/667	Not reported	Not reported	Complications

Appendix 3. Treatment of varicose veins. Excluded articles
Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation)

Study (author, publication year)	**Reason for exclusion**
Benarroch-Gampel 2013	Not correct PICO (Not specified that all patients had verified truncal reflux)
Carradice 2014	Not correct PICO (Comparison of symptomatic and non-symptomatic patients)
Darvall 2014	Not correct PICO (Mixed patient population)
Dermody 2013	Systematic review with no additional included studies reported outcomes compared with NICE guidance
Dermody 2014	Systematic review with no additional included studies reported outcomes comapred with NICE guidance
Gan 2013	Not correct PICO (Surgical procedure and EVLA combined in the intervention group)
Kalodiki 2012	Not correct PICO (Surgical procedure and UGFS combined in the intervention group)
Kuhlmann 2013	Cost-saving analysis. Commented upon in the Economy section.
Kulkarni 2013	Not correct PICO (Not specified that all patients had verified truncal reflux)
Lattimer 2013b	Cost-effectiveness analysis. Commented upon in the Economy section.
Moreno-Moraga 2013	Not correct PICO (Another patient population and different interventions)
Mozafar, 2014	Not correct PICO - Incorrect C (high ligation only)
Pan 2014	Systematic review with no additional included studies reported outcomes compared with NICE guidance
Samuel (Phlebology)2013b	Case series with less than 350 patients/limbs.
Sarvananthan 2012	Not correct PICO (Not specified that all patients had verified truncal reflux)
Shadid 2014	Not clear that all patients had verified truncal reflux.
Sutton 2012	Not correct PICO (Not specified that all patients had verified truncal reflux)
Yang 2013	Not correct PICO (Unusual type of endothermal treatment)
Yilmaz 2012	Not correct PICO (EVLA and UGFS combined)

Appendix 4.1.1
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Health related quality of life.

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients /legs	With drawals - drop-outs/ legs (n)	Results: Endothermal ablation	Results: Conventional surgery	Comments	Directness*	Study limitations *	Precision *
NICE	HTA-report	3 RCTs	Not stated	Global quality of life 1-12w SMD 0.43 lower (0.84 to 0.02 lower)	Reference	1 study used AVVQ 2 studies used CIVIQ-2	GRADE VERY LOW		
		1 RCT	-	Global quality of life 1y SMD 0.04 higher (0.51 lower to 0.42 higher)	Reference	CIVIQ-2 used	VERY LOW		
		1 RCT		Global quality of life 2y SMD 0.11 higher (0.35 lower to 0.56 higher)	Reference	CIVIQ-2 used	VERY LOW		
Biemans 2013 Netherlands & Belgium	RCT: EVLA CS	 n = 80 n = 80	 n = 4 n = 15	CIVIQ score Difference between groups at end of follow-up: -2.0 (95% CI: -6,4;2.4) EQ-5D Difference between groups at end of follow-up: 0.01 (95% CI: -0.02;0.04)		Follow-up 12 months	?	?	+
Rasmussen 2013a (J Vasc Surg) Denmark	RCT: EVLA CS	 n=62 n=59	 n=20 n=19	AVVQ Baseline: 18.3 (sd 8.8) 60 months: 3.0 (sd 5.3) NS between the groups. SF-36 NS between the study groups in any of the SF-domains	AVVQ Baseline: 16.0 (sd 6.3) 60 months: 3.6 (sd 4.1) SF-36 NS between the study groups in any of the SF-domains	Only patients with clinical recurrence were assessed for reflux 1/3 dropped out!	?	-	?
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT: RFA EVLA CS	 n=125/144 n=125/ 148 n=124/143	 n=39/52 n=37/53 n=38/50	AVVQ RF: Baseline: 18.7 (sd 8.6) 3 years: 4.4 (sd 6.6) EVLA: Baseline: 18.4 (sd 9.1) 3 years: 4.6 (sd 5.8) NS between the study groups.	AVVQ Baseline: 19.3 (SD 8.5) 3 years: 4.0 (SD 4.9)	Approximately 30% did not come to follow-up	+	-	?

Appendix 4.1.1
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Health related quality of life. 2(2)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients /legs	With drawals - drop-outs/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
				Endothermal ablation	Conventional surgery				
Roopram 2013 Netherlands	RCT: EVLA CS	n=118 n=57	Not reported	AVVQ Mean Baseline 16.0 (sd 10.0) 2 weeks 16.8 (sd 7.7) 6 weeks 9.0 (sd 7.7) NS between the study groups	AVVQ Mean Baseline 11.9 (sd 5.8) 2 weeks 16.4 (sd 8. 9) 6 weeks 8.7 (sd 8.0)	SSV treatment only. PP analysis between groups . Short follow-up.	?	?	+

Footnotes and abbreviations: AVVQ = Aberdeen Varicose Vein Questionnaire = Aberdeen Varicose Vein Symptoms Severity Score (AVVS); score 0-100, the lower the better. CIVIQ = Chronic Venous Insufficiency Questionnaire; score 0-100, the lower the better. EQ-5D = EuroQual 5D. SF-36 = Short Form Health Survey 36; the higher score the better. SMD = Standardised mean difference, RCT = Randomised, controlled trial. CI = Confidence interval, NS = Non-significant, PP = per protocol, EVLA = Endovenous Laser Ablation. RFA = Radiofrequency ablation. CS = Conventional surgery, SSV = small saphenous vein.

Appendix 4.1.2
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Presence of Saphenous Vein Reflux. 1 (1)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients /legs	With drawals - drop-Outs/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
				Endothermal ablation	Conventional surgery				
NICE	HTA-report	8 RCTs 6 RCTs		<u>0 - 12 weeks</u> 17/751 (2.3%) RR = 0.48 (95% c.i. 0.14 to 1.64) <u>1 – 3 years</u> 36/513 (7.0%) RR = 1.26 (95% c.i. 0.71 to 2.24)	<u>0 - 12 weeks</u> 24/542 (4.4%) <u>1 – 3 years</u> 19/342 (5.6%)		<u>GRADE</u> VERY LOW VERY LOW		
Biemans 2013 Netherlands & Belgium	RCT: EVLA CS	 n=80 n=80	 n=2 n=12	9/78 (11.5 %) NS between study groups	8/68 (11.8 %)	Follow-up 12 months	?	?	+
Flessenkamper 2013 Germany	RCT: EVLA CS	 n=142 n=159	 n=15 n=31	8.7 % NS between study groups	3.1 %	Follow-up 6 months Sapheno-femoral junction + treated vein	-	+	+
Rasmussen 2013a (J Vasc Surg) Denmark	RCT: EVLA CS	 n=62/69 n=59/68	 n=20/21 n=19/24	9 (17.9 %)* NS between study groups	4 (10.1 %)*	Follow-up 5 years * Kaplan Meier estimate Patients only scanned if they had a clinical recurrence	?	-	?
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT: RFA EVLA CS	 n=125/144 n=125/148 n=124/143	 n=39/52 n=37/53 n=38/50	**RFA** 15% * **EVLA** 20% *	20% *	Follow-up 3 years * Kaplan Meier estimate More than 50 % of patients without previous recurrence did undergo the final examination. Only legs with clinical recurrence were scanned. Recurrence regarded cumulated clinical recurrence	+	-	?

Footnotes and abbreviations: RCT = Randomised, controlled trial, RR = Relative risk, NS = Non-significant. EVLA = Endovenous Laser Ablation. RFA = Radiofrequency ablation., CS = Conventional surgery.

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Appendix 4.1.3.
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Time to return to work.

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients	With drawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision *
				Endothermal ablation	Conventional surgery				
NICE	HTA-report	2 RCT		**RFA** Mean (sd) RCT #1 : 6.5 (sd 3.3) days RCT #2: 4.7 (sd 11.9) days Mean difference (1+2): -8.6 (95% CI: -11.6 to – 5.6)	Mean (sd) RCT #1: 15.6 (sd 6.0) days RCT # 2: 12.4 (sd 11.6) days		GRADE LOW		
		2 RCT		**EVLA** Mean (sd) RCT #1 : 7.0 (sd 6.0) days RCT #2: 4.4 (sd 5.4) days Mean difference (1+2): -0.2 (95% CI: -1.4 to + 1.1)	Mean (sd) RCT #1 : 7.6 (sd 4.9) days RCT #2: 4.2 (sd 3.7) days		LOW		
Roopram 2013 Netherlands	RCT: EVLA CS	n=118 n=57	Not reported	<u>After 2 weeks:</u> 97.6 % p < 0.05 between study groups	<u>After 2 weeks:</u> 89 %	Daily work and activities	?	?	+

Footnotes and abbreviations: RCT = Randomised, controlled trial, CI = Confidence interval, NS = Non-significant, EVLA = Endovenous Laser Ablation. RFA = Radiofrequency ablation. CS = Conventional surgery

Appendix 4.1.4.
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Postoperative pain (0 – 14 days). 1(1)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients	With drawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision *
				Endothermal ablation	Conventional surgery				
NICE	HTA-report	8 RCTs		**EVLA** <u>First 24 hours:</u> 3.6 (sd 2.6) Mean difference between groups= -0.42 (95% CI:-1.27 to + 0.43) <u>Up to 10-14 days:</u> RCT 1 in SR: 1.7 (sd 2.0) RCT 2 in SR: 2.6 (sd 2.4) Mean difference between groups: 0.58 (95% CI:0.17 to 1.0)	<u>First 24 hours:</u> 4.0 (sd 2.3) <u>Up to 10-14 days:</u> RCT 1 in SR: 0.8 (sd 1.5) RCT 2 in SR: 2.3 (sd 2.2)	VAS scale 0 -10 (10 worst)	<u>GRADE</u> VERY LOW		
				RFA <u>Up to 10-14 days:</u> RCT 2 in SR: 1.2 (sd 1.7) RCT 3 in SR: 0.7 (sd 0.5) Mean difference between groups: 1.0 (95% CI:0.62 to 1.4)	 <u>Up to 10-14 days:</u> RCT 2 in SR: 2.5 (sd 2.2) RCT 3 in SR: 1.7 (sd 1.3)		LOW		
Roopram 2013 Netherlands	RCT: EVLA CS	n=118 n=57	Not reported	<u>At 7 days:</u> 31 (sd 26) p< 0.05 between study groups <u>At 2 weeks:</u> 18 (sd 23) NS between study groups	<u>At 7 days:</u> 18 (sd 25) <u>At 2 weeks:</u> 15 (sd 20)	VAS scale (0 -100, 100 worst)	?	?	+

Footnotes and abbreviations: RCT = Randomised, controlled trial. CI = Confidence interval, NS = Non-significant. EVLA = Endothermal Venous Laser Ablation. RFA = Radiofrequency ablation. CS = Conventional surgery,VAS = Visual Analogue Scale.

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Appendix 4.1.5.
Treatment of varicose veins. PICO 1 = Endothermal ablation versus Conventional surgery.
Outcome variable: Venous clinical severity score (VCSS). VCSS scale 0 – 33, 33 worst.

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients/ legs	With drawals - dropouts /legs (n)	Results		Comments	Directness*	Study limitations	Precision *
				Endothermal ablation	Conventional surgery				
NICE	HTA-report	1 RCT RF vs. CS		<u>Up to 50 days post-intervention:</u> Δ = -5.1 (sd 1.5) Mean difference between study groups: -0.70 (95% CI:-1.67 to + 0.27) <u>At 3 years:</u> Δ = -4.3 (sd 2.3) Mean difference between study groups: -0.3 (95% CI:-1.63 to + 1.03)	<u>Up to 50 days post-intervention:</u> Δ = -4.4 (sd 1.1) <u>At 3 years:</u> Δ = -4.0 (sd 1.2)		<u>GRADE</u> LOW VERY LOW		
Rasmussen 2013a (J Vasc Surg) Denmark	RCT: EVLA CS	n=62/69 n=59/68	n=20/21 n=19/24	Baseline: 2.8 (sd 1.7) At 5 years: 0.4 (sd 0.9) NS between study groups	Baseline: 2.4 (sd 1.4) At 5 years: 0.4 (sd 0.9)	Very low baseline scores indicating a selected patient population or systematic bias in the use of VCSS. Less than half of the patients examined at 5 years	+	-	?
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT: EVLA RFA CS	n=125/144 n=125/148 n=124/143	n=39/52 n=37/53 n=38/50	**EVLA** Baseline: 2.7 (sd 2.3) At 3 years: 0.3 (sd 1.3) NS between study groups **RFA** Baseline: 3.0 (sd 2.1) At 3 years: 0.4 (sd 1.8) NS between study groups	Baseline : 2.8 (sd 1.6) At 3 years: 0.3 (sd 0.5)	Very low baseline scores indicating a selected patient population or systematic bias in the use of VCSS. Less than one third of the patients examined at 3 years.	?	-	?

Footnotes and abbreviations: RCT = Randomised, controlled trial, Δ = change from baseline, NS = Non-significant, EVLA = Endothermal Venous Laser Ablation. RFA = Radiofrequency ablation. CS = Conventional surgery.

Appendix 4.2.1
Treatment of varicose veins. PICO 2 = Foam sclerotherapy versus Conventional surgery.
Outcome variable: Health related quality of life. 1(2)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients/ legs	With drawals - dropouts/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
				Foam sclerotherapy	Conventional surgery				
NICE	HTA-report	2 RCT	Not stated	<u>SF-36 Physical</u> At 1 year: 53.3 (sd 5.9) Mean difference between study groups: 1.4 (95% CI:-0.3 to 3.1) <u>SF-36 Mental</u> At 1 year: 53.8 (sd 6.3) Mean difference between study groups: 1.1 (95% CI:-0.8 to 3.0) <u>EQ 5D</u> Δ = + 0.06 (sd 0.2)	<u>SF 36 Physical</u> At 1 year: 51.9 (sd 7.6) <u>SF-36 Mental</u> At 1 year: 54.7 (sd 8.9) <u>EQ 5D</u> Δ = + 0.06 (sd 0.2)	SF-36 PCS (Physical component score) scale 0 – 100, 100 best For SF-36 one RCT, and for EQ 5D another RCT Follow-up 2 years	<u>GRADE</u> MODERATE MODERATE LOW		
Biemans 2013 Netherlands & Belgium	RCT UGFS CS	 n = 80 n = 80	 n = 15 n = 3	<u>CIVIQ</u> Baseline: 24.0 (sd 20.7) Mean difference between study groups at 12 months: 0.7 (−4.9 to 3.6) <u>EQ-5D</u> Baseline: 0.8 (sd 0.2) Mean difference between study groups at 12 months: 0.01 (−0.02 to 0.04)	CIVIQ Baseline: 25.1 (sd 19.2) <u>EQ-5D</u> Baseline: 0.9 (sd 0.1)	Follow-up 12 months 15/80 (19%) randomized to CS did not receive CS	?	?	+

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients/ legs	With drawals - dropouts/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS CS	n = 125/145 n = 125/143	At 1 year: n = 17/22 n = 24/31 At 3 years: n = 14/23 n = 38/50	<u>SF- 36 PCS</u> Baseline: 48.2 (sd 8.0) At 1 year: 52.1 (sd 7.4) <u>SF- 36 MCS</u> Baseline: 55.1 (sd 89) At 1 year: 54.9 (sd 8.2) <u>AVVQ</u> Baseline: 18.4 (sd 9.1) At 3 years: 4.8 (sd 5.7) All outcomes NS between study groups	<u>SF- 36 PCS</u> Baseline: 49.2 (sd 7.9) At 1 year: 53.5 (sd 5.9) <u>SF- 36 MCS</u> Baseline: 53.0 (sd 9.0) At 1 year: 55.7 (sd 6.3) <u>AVVQ</u> Baseline: 19.3 (sd 8.4) At 3 years: 4.0 (sd 4.9)	Approximately 40- 50 % of all patients were lost to follow-up in all groups	?	-	?

Footnotes and abbreviations: AVVQ = Aberdeen Varicose Vein Questionnaire = Aberdeen Varicose Vein Symptoms Severity Score (AVVS); score 0-100, the lower the better. CIVIQ = Chronic Venous Insufficiency Questionnaire; score 0-100, the lower the better. EQ-5D = EuroQual 5D. SF-36 = Short Form Health Survey-36; the higher score the better;PCS = Physical component score & MCS = Mental component score, RCT = Randomised, controlled trial, CI = Confidence inter val, NS = Non-significant, Δ = change from baseline, UGFS = Ultrasound Guided Foam Sclerotherapy, CS = Conventional surgery.

Appendix 4.2.2.
Treatment of varicose veins. PICO 2 = Foam sclerotherapy versus Conventional surgery.
Outcome variable: Presence of reflux. 1(1)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients /legs	With drawals - dropouts/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
				Foam sclerotherapy	Conventional surgery				
NICE	HTA-report	4 RCT	Not stated	<u>After 3- 12 months</u> 155/547 (28.3%) RR =0.46 (95% CI: 0.25 to 0.84)	<u>After 3- 12 months</u> 63/419 (15%)		<u>GRADE</u> LOW		
Biemans 2013 Netherlands & Belgium	RCT UGFS CS	 n = 80 n = 80	 n = 15 n = 3	21/80 (27 %)	7/80 (10 %)	Follow-up 1 year Difficulties to recruit to open surgery Different presentation of the outcome in the study groups	?	?	+
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS CS	 n = 125/145 n = 125/143	At 3 years: n = 14/23 n = 38/50	26.4 % p < 0.001 between study groups	6.5 %	Percentage is the Kaplan-Meier estimate Follow-up 3 years	+	-	?

Appendix 4.2.3
Treatment of varicose veins. PICO 1 = Foam sclerotherapy versus Conventional surgery.
Outcome variable: Time to return to work.

Author, year, country	Study design	Number of studies/ Number of patients	With drawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision *
				Foam sclerotherapy	Conventional surgery				
NICE	HTA-report	1 RCT	Not stated	Median 2.9 days (IQR: 0-33)	Median 4.3 days (IQR: 0-42)	Risk of bias deemed very serious IQR, inter-quartile range	<u>GRADE</u> Not applicable		

Footnotes and abbreviations: RCT = Randomised, controlled trial, RR = Relative risk,CI = Confidence interval, NS = Non-significant, Δ = change from baseline, UGFS = Ultrasound Guided Foam Sclerotherapy, CS = Conventional surgery.

Appendix 4.2.4.
Treatment of varicose veins. PICO 2 = Foam sclerotherapy versus Conventional surgery.
Outcome variable: Postoperative pain

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of patients	With drawals - dropouts/ legs (n)	Results		Comments	Directness*	Study limitations	Precision *
				Foam sclerotherapy	Conventional surgery				
NICE	HTA-report	2 RCT		RCT #1 VAS score 1.6 (sd 2.0) Mean difference between study groups: 0.7 (95% CI: -0.2 to 1.2) 2 RCT: No of pats 15/59 (25 %) RR: 0.32 (95% CI 0.20 to 0.52)	RCT #1 VAS score 2.3 (sd 2.2) 2 RCT: No of pats 72/90 (80 %)	VAS 0-10; The lower the better	GRADE LOW LOW		

Appendix 4.2.5
Treatment of varicose veins. PICO 2 = Foam sclerotherapy versus Conventional surgery.
Outcome variable: Venous clinical severity score (VCSS).

Author, year, country	Study design	Number of studies/ Number of patients	With drawals - dropouts	Results		Comments	Directness*	Study limitations	Precision *
				Foam sclerotherapy	Conventional surgery				
NICE	HTA-report	1 RCT	Not stated	At 2 yeas: Δ = -1.8 (sd 2.1) Mean difference between study groups: -0.3 (95% CI: -0.69 to + 0.17)	At 2 years: Δ = -1.5 (sd 2.1)		GRADE LOW		
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS CS	 n = 145 n = 143	 14/23 38/50	Baseline: 2.7 (sd 1.5) At 3 years: 0.2 (sd 0.4) NS between study groups	Baseline: 2.8 (sd 1.6) At 3 years: 0.3 (sd 0.5)	The frequency of reoperations differed between the study groups. In UGFS 31% and in CS 15 %. (Kaplan Meier estimate)	?	-	?

Appendix 4.3.1.
Treatment of varicose veins. PICO 3 = Foam sclerotherapy versus Endothermal ablation.
Outcome variable: Health related quality of life (HRQoL). 1(2)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of legs	With drawals - dropouts/ legs (n)	Results: Foam sclerotherapy	Results: Endothermal ablation	Comments	Directness*	Study limitations	Precision
NICE	SR (HTA report)	1 RCT 1 RCT	Not stated	<u>SF-36 Physical</u> 51.9 (sd 7.7) <u>AVVQ</u> Median Δ = -9 (IQR=11) All outcome variables ns between study groups	**EVLA** <u>SF-36 Physical</u> 52.6 (sd 6.0) <u>AVVQ</u> Median Δ = -12 (IQR=11)	**RFA** <u>SF-36 Physical</u> 53.2 (sd 5.3)	Follow-up 12 months Follow-up 3 months	<u>GRADE</u> LOW		
Biemans 2013 Netherlands & Belgium	RCT UGFS vs EVLA	n =80 n =80	See comments	<u>CIVIQ-score</u> Mean Δ = -0.66 (95% CI:-4.89 to 3.57) <u>EQ-5D</u> Mean Δ = 0.01 (95% CI:-0.02 to 0.04) <u>Health (a supplement of EQ-5D)</u> Δ = -1.97 (95% CI:-4.78 to 0.84) All outcome variables were NS between study groups	**EVLA** <u>CIVIQ-score</u> Mean Δ = -1.93 (95% CI:-6.36 to 2.49) <u>EQ-5D</u> Mean Δ = 0.01 (95% CI:-0.02 to 0.04) <u>Health (a supplement of EQ-5D)</u> Δ = 1.61 (95% CI:-1.67 to 4.89)		Follow-up 12 months UGFS patients were seven years older than EVLA patients. 14 pat missing data for CIVIQ, 24 excluded with different bilateral randomized treatment. 24 pat missing data for EQ-5D and Health, 24 excluded with different bilateral randomized treatment	?	?	?

Footnotes and abbreviations: AVVQ = Aberdeen Varicose Vein Questionnaire = Aberdeen Varicose Vein Symptoms Severity Score (AVVS); score 0-100, the lower the better. SF-36 = Short Form Health Survey 36; the higher score the better, UGFS =Ultrasound-guided foam sclerotherapy, EVLA =Endovenous laser ablation), RFA =Radiofrequency ablation, CS= Conventional surgery, SR = Systematic review, RCT = Randomized controlled trial), Δ = change between baseline and end of study, NS = Non-significant, CI = confidence interval, IQR= Interquartile Range

Appendix 4.3.1.
Treatment of varicose veins. PICO 3 = Foam sclerotherapy versus Endothermal ablation.
Outcome variable: Health related quality of life (HRQoL). 2(2)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of legs	With drawals - dropouts/ legs (n)	Results			Comments	Directness*	Study limitations	Precision
				Foam sclerotherapy	Endothermal ablation					
Lattimer 2013 UK	RCT UGFS vs EVLA	 n =50 n =50	 n =6 n =4	<u>AVVQ</u> Baseline: 24.3 (IQR:16.3 -30.0) At 15 months: 9.5 (IQR: 2.4 – 15.6) NS between study groups	**EVLA** <u>AVVQ</u> Baseline: 20.0 (IQR: 14.0 – 27.9) At 15 months: 12.2 (IQR: 6.8 - 18.0)			+	+	+
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS vs EVLA vs RFA	 n =144 n =144 n =148	 14/23 39/52 37/53	<u>SF-Physical</u> Baseline: 48.2 (sd 8.0) At 3 years: 51.9 (sd 8.1) <u>AVVQ</u> Baseline: 18.4 (sd 9.0) At 3 years: 4.8 (sd 5.7) Both outcome variables NS between study groups	**EVLA** <u>SF-Physical</u> Baseline: 48.2 (sd 8.0) At 3 years: 51.9 (sd 8.1) <u>AVVQ</u> Baseline: 18.0 (sd 9.0) At 3 years: 4.6 (sd 5.8)	**RFA** <u>SF-Physical</u> Baseline: 49.1 (sd 8.4) At 3 years: 50.7 (sd 7.8) <u>AVVQ</u> Baseline: 18.7 (sd 8.6) At 3 years: 4.4 (sd 6.6)		+	-	?

Footnotes and abbreviations: AVVQ = Aberdeen Varicose Vein Questionnaire = Aberdeen Varicose Vein Symptoms Severity Score (AVVS); score 0-100, the lower the better. SF-36 = Short Form Health Survey 36; the higher score the better, UGFS =Ultrasound-guided foam sclerotherapy, EVLA =Endovenous laser ablation), RFA =Radiofrequency ablation, CS= Conventional surgery, SR = Systematic review, RCT = Randomized controlled trial), Δ = change between baseline and end of study, NS = Non-significant, CI = confidence interval, IQR= Interquartile Range

Appendix 4.3.2.
Treatment of varicose veins. PICO 3 = Foam sclerotherapy versus Endothermal ablation.
Outcome variable: Presence of truncal reflux 1(1)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of legs	With drawals - dropout/ legs (n)	Results		Comments	Directness*	Study limitations *	Precision *
				Foam sclerotherapy	Endothermal ablation				
NICE	SR (HTA report)	1 RCT		Reflux above knee 20/123 (16.3%)	**EVLA** 7/121 (5.8%) RR vs UGFS: 2.81 (95% CI: 1.23 to 6.4)	**RFA** 6/124 (4.8%) RR vs UGFS: 3.36 (95% CI: 1,4 - 8,08)	Follow-up 1 year	GRADE MODERATE		
Biemans 2013 Netherlands & Belgium	RCT UGFS vs EVLA	n =80 n =80	n =24 n =11	GSV at the level of midthigh 27.3% p < 0.02 between study groups	GSV at the level of midthigh 11.53%		12 months follow-up. UGFS patients seven years older than EVLA patients	?	?	+
Lattimer 2013a UK	RCT UGFS vs EVLA	n =50 n =50	n =6 n =4	GSV at some point in the thigh 32.6% p = 0.001 between study groups	GSV at some point in the thigh 4.5%		15 months follow-up	+	+	+
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS vs EVLA vs RFA	n =144 n =144 n =148	14/23 39/52 37/53	Refluxing segments of 10 cm or more 26.4% p< 0.0001 between UGFS and the other study groups	**EVLA** Refluxing segments of 10 cm or more 6.8%	**RFA** Refluxing segments of 10 cm or more 7.0%	3 years follow-up	+	-	?

Footnotes and abbreviations: UGFS =Ultrasound-guided foam sclerotherapy, EVLA =Endovenous laser ablation), RFA =Radiofrequency ablation, CS= Conventional surgery, GSV = Great Saphenous Vein, SR = Systematic review, RCT = Randomized controlled trial, RR = Relativ risk, NS = Nonsignificant

Appendix 4.3.3.
Treatment of varicose veins. PICO 3 = Foam sclerotherapy versus Endothermal ablation.
Outcome variable: Postoperative pain 1(1)

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of legs	With drawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision *
				Foam sclerotherapy	Endothermal ablation				
NICE	SR (HTA report)	1 RCT	Not stated	<u>VAS</u> 1.6 (sd 2.0)	**EVLA (1)** <u>VAS</u> 2.6 (sd 2.4) Mean difference vs UGFS = 1.0 (95% CI: -0.5 to 1.5)	**RFA (2)** <u>VAS</u> 1.2 (sd 1.7) Mean difference vs UGFS = -0.4 (95% CI: -0.1 to 0.8)	Pain after 10 days	<u>GRADE</u> LOW (1) MODERATE (2)		

Footnotes and abbreviations: , VAS = Visual analogue scale (score 1 – 10), UGFS =Ultrasound-guided foam sclerotherapy, EVLA =Endovenous laser ablatio), MD= Mean difference (95% CI), EMA = Endovenous Microvave Ablation, RFA =Radiofrequency ablation, CS= Conventional surgery, SR = Systematic review, RCT = Randomized controlled trial, CI = Confidence interval.

Appendix 4.3.4.
Treatment of varicose veins. PICO 3 = Foam sclerotherapy versus Endothermal ablation.
Outcome variable: Venous clinical severity score (VCSS). VCSS scale 0 – 33, 33 worst

* + No problem
? Some problems
- Major problems

Author, year, country	Study design	Number of studies/ Number of legs	With drawals - dropouts	Results		Comments	Directness*	Study limitations	* Precision
				Foam sclerotherapy	Endothermal ablation				
NICE	SR (HTA report)	1 RCT		VCSS Δ = -4 (IQR: 3)	VCSS Δ = -4 (IQR: 3)	Follow-up 3 months	GRADE Not applicable		
Lattimer 2013a UK	RCT UGFS vs EVLA	 n =50 n =50	 n =6 n =4	VCSS Baseline: Median 6 (IQR:5 - 9) At 15 months: Median 5 (IQR: 3 –6) NS between study groups	**EVLA** VCSS Baseline: Median 6 (IQR:5 - 8) At 15 months: Median 5 (IQR: 3 - 6)		+	+	+
Rasmussen 2013b J Vasc Surg: Venous and Lymph Dis) Denmark	RCT UGFS vs EVLA vs RFA	 n =144 n =144 n =148	 n =73 n =83 n =74	VCSS Baseline: 2.7 (sd 1.5) At 3 years: 0.2 (sd 0.4) NS between study groups	**EVLA** VCSS Baseline. 2.7 (sd 2.2) At 3 years: 0.2 (sd 0.4)	**RFA** VCSS Baseline: 3.0 (sd 2.0) At 3 years: 0.4 (sd 1.8)	+	-	?

Footnotes and abbreviations: VCSS = Venous clinical severity score, UGFS =Ultrasound-guided foam sclerotherapy, EVLA =Endovenous laser ablation), RFA =Radiofrequency ablation, SR = Systematic review, RCT = Randomized controlled trial), Δ = change between baseline and end of study, NS = Non-significant, IQR= Interquartile Range

Appendix 5a – Treatment of varicose veins. Complications - Pulmonary embolism, Deep Vein Thrombosis, Phlebitis. (Gray field: technique not studied, - denotes not reported)

Author, Year, Country	Study design	Time of follow-up	Pulmonary embolism				Deep venous thrombosis				Phlebitis				Comments
			RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	
NICE Clinical Guidelines 2013 UK	Systematic review of RCTs	Various	0 % (0/395)		0.4% (3/764)	0 % (0/612)	0.2 % (3/1255)		1.5 % (12/784)	0.4 % (5/1267)	9.8 % (64/650)		9.7 % (57/586)	2.1% (13/622)	
Biemans 2013 Netherlands & Belgium	RCT	3 months		0 % (0/78)	0 % (0/77)	0 % (0/68)		0 % (0/78)	0 % (0/77)	0 % (0/68)		3.8 % (3/78)	3.9 % (3/77)	5.9 % (4/68)	
Lattimer 2013 UK	RCT	15 months		0 %	0 %			0 %	0 %			"Many pts"	"Many pts"		
Roopram 2013 Netherlands	RCT	6 weeks		-		-		0.8 % (1/110)		0 % (0/52)		-		-	
Samuel 2013 UK	RCT	1 year		-		-		0 % (0/53)	0.3 % (1/337	1.9 % (1/53)		-	-	-	
Asciutto 2012 Sweden	Case series	Up to 4 years			0.3 % (1/337)				)						
Braithwaite 2013 7 European countries	Case series	0.5 – 1 year	0.1 % (2/2987)	0 % (0/977)			1.5 % (44/ 2987)	1.7 % (17/977)			-	-			
Chi 2014 USA	Case series	1 week		-				5.3 % (19/360)				-			
Harlander-Locke 2013	Case series	24 -72 hours	0.1 % (1/735)				-				-				
Kane 2014 USA	Case series	Not reported		-				5.6 %* (29/522)				-			*EHIT

Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), EMA (= Endovenous Microvave Ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life), - = Not reported, EHIT = Endothermal Heat Induced Thrombosis

Appendix 5a – Treatment of varicose veins. Complications - Pulmonary embolism, Deep Vein Thrombosis, Phlebitis. (Gray field: technique not studied, - denotes not reported)

Author, Year, Country	Study design	Time of follow-up	Pulmonary embolism				Pulmonary embolism				Pulmonary embolism				Comments
			RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	
Moul 2014 USA	Case series	11.4 months (mean)		0 % (0/1171)				0 % (0/1171)			-	-			
Newman 2014 UK	Case series	1 year	0 % (0/520)				0 % (0/520)								
Rhee 2013 USA	Case series	1,7 days (1-8)	-	-			2.1 %* (6/285)	6.4 %* (15/234)			-	-			* EHIT
Sadek 2103 USA	Case series	16 weeks (mean)	0.1 % (2/4223)				2.1 %* (89/4223)				0.8 % (33/4223)				* EHIT
Sufian 2013	Case series	2 – 3 days	0.03%				3.0 %*				-				* EHIT
Sufian 2014	Case series	2 – 3 days		0 %				0.9 %*				-			* EHIT
Tolva 2013 Italy	Case series	Up to 1 year	0 % (0/407)				0 % (0/407)				1 % (4/407)				
Zuniga 2012 USA	Case series	1 year	-				1.9 % (11/581)				14.1 % (82/581)				

Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), EMA (= Endovenous Microvave Ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life), - = Not reported, EHIT = Endothermal Heat Induced Thrombosis

Appendix 5b – Treatment of varicose veins. Complications – Nerve injury, Skin discoloration, Post procedure pain. (Gray field: technique not studied, - denotes not reported)

Author, Year, Country	Study design	Time of follow-up	Nerve injury				Skin discoloration				Post procedure pain				Comments
			RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	RFA	EVLA	UFGS	CS	
NICE Clinical Guidelines 2013 UK	Systematic review of RCTs	Various	5.2 % (74/1433)		0.7% (4/613)	8.1 % (106/1303)	3.1 % (26/822)		16.9 % (129/764)	7.0 % (59/838)	14.9 % (48/323)		37.1 % (88/237)	40.7 % (208/511)	
Biemans 2013 Netherlands & Belgium	RCT	3 months		-	-	-		2.6 % (2/78)	1.3 % (1/77)	0 % (0/68)		-	-	-	
Flessenkamper 2013 Germany	RCT	6 months		18.0 %		4.0 %		11.0 %		9.4 %		-		-	
Lattimer 2013 UK	RCT	15 months		0 %	0 %			"Many pts"	"Many pts"			-	-		
Roopram 2013 Netherlands	RCT	6 weeks		6.7 % (7/110)		31.0 % (16/52)		-		-		-		-	
Samuel 2013 UK	RCT	1 year		3.7 % (2/53)		9.4 % (5/53)		-		-		-		-	
Moul 2014 USA	Case series	11.4 months (mean)		0 % (0/1171)				-				-			
Newman 2014 UK	Case series	1 year	-				0 % (0/520)				-				
Sadek 2103 USA	Case series	16 weeks (mean)	0 % (0/4223)				-	-			-	-			

Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), EMA (= Endovenous Microvave Ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life), - = Not reported.

Appendix 5c – Treatment of varicose veins. Complication – Wound infection (Gray field: technique not studied, - denotes not reported)

Author, Year, Country	Study design	Time of follow-up	Wound infection			
			RFA	EVLA	UFGS	CS
Biemans 2013 Netherlands & Belgium	RCT	3 months		0 % (0/78)	0 % (0/77)	4.4 % (3/68)
Roopram 2013 Netherlands	RCT	6 weeks		0 % (0/110)		11.5 % (6/52)
Kane 2014 USA	Case series	Not reported		0 % (0/520)		
Sadek 2103 USA	Case series	16 weeks (mean)	0 % (0/4223)			Sadek 2103 USA

Abbreviations: UGFS (=Ultrasound-guided foam sclerotherapy, EVLA (=Endovenous laser ablation), EMA (= Endovenous Microvave Ablation), RFA (=Radiofrequency ablation), CS (= Conventional surgery), RCT (= Randomized controlled trial), CEAP (=Clinical, etiological, anatomical and pathological classification), HRQoL (= Health Realted Quality of Life), - = Not reported.

Appendix 6 ETHICAL ANALYSIS OF

Question	Answer/ comment
1. From the patient's perspective, how does endovenous treatment of varicose veins affect the patient's quality of life and life expectancy?	Not at all.
2. How severe is the patient´s need that endovenous treatment of varicose veins must meet?	Results must be equal to conventional surgery with less invasiveness
3. Does endovenous treatment of varicose veins have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	No
4. Can endovenous treatment of varicose veins affect the patient’s ability and possibility to be independent?	No
5. If implemented, does endovenous treatment of varicose veins require any special steps to not compromise the patient's autonomy?	No
6. How does endovenous treatment of varicose veins affect the patient’s physical, moral and personal integrity?	None
7. Is endovenous treatment of varicose veins cost-effective?	Yes
8. How endovenous treatment of varicose veins affect resources?	It reduces the need for operation theatres as the workload is transferred to the outpatient clinic where resources have to increase.
9. Is endovenous treatment of varicose veins in conflict with professional values?	No

10. Does endovenous treatment of varicose veins change the role of the professional in relation to the patient?	It increases communication between the patient and the surgeon as it is conducted in local anaesthesia.
11. Does endovenous treatment of varicose veins affect, or does it put any new demands on, a third party?	No
12. Is there any legislation of relevance with regard to? endovenous treatment of varicose veins	No
13. Is there any risk of conflict between the procedure of endovenous treatment of varicose veins and values of the society, or values of different groups?	No
14. Is there a risk that an introduction of endovenous treatment of varicose veins will cause a conflict with particular interests?	No
15. Can an introduction of endovenous treatment of varicose veins influence the trust of the health care system?	No
CONCLUSIONS	There are no ethical considerations against the use of endovenous treatment of varicose veins.

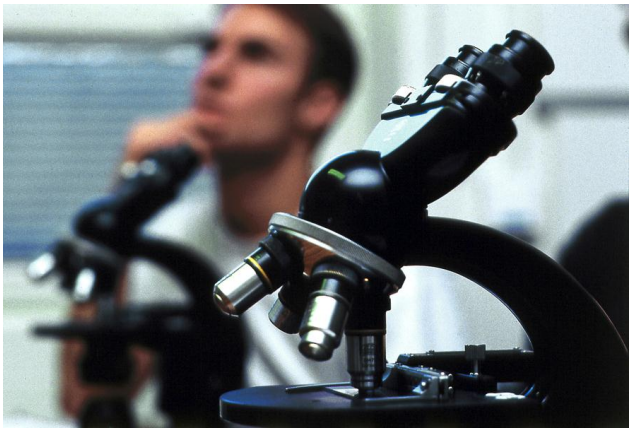
Appendix 7

The capacity estimation of conventional surgeries is based on an average use of operating theatre for 1.5 hours per intervention and that 4 legs could be treated per day. For endovenous treatment, the capacity estimation is based on a visit at the day care for an average of 45 minutes per intervention and that 6 legs could be treated per day. An assumption is made that varicose veins interventions are performed during 40 weeks per year. With the present procedure and with an average weekly estimation, the operating theatres are use for 23 hours and 15 patients are treated with conventional surgery and for endovenous treatment eight patient are treated with visits at the day care for four hours. The second scenario estimation would result in a reduction of use of operation theatre of 5 hours per week and 200 hours per year, meanwhile 60 more patient could be treated on an annual basis.

	HOURS PER WEEK WITH SURGERY	**WEEKLY PATIENT** WITH SURGERY	**HOURS PER WEEK** WITH RFA/EVLA	**WEEKLY PATIENT** WITH RFA/EVLA	**TOTAL ANNUAL PATIENTS IN REGION VÄSTRA GÖTALAND**
PRESENT	23	15	4	8	**900**
SCENARIO 1	21	14	5	9	**920**
SCENARIO 2	18	12	6	12	**960**
SCENARIO 3	9	6	11	21	**1080**

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

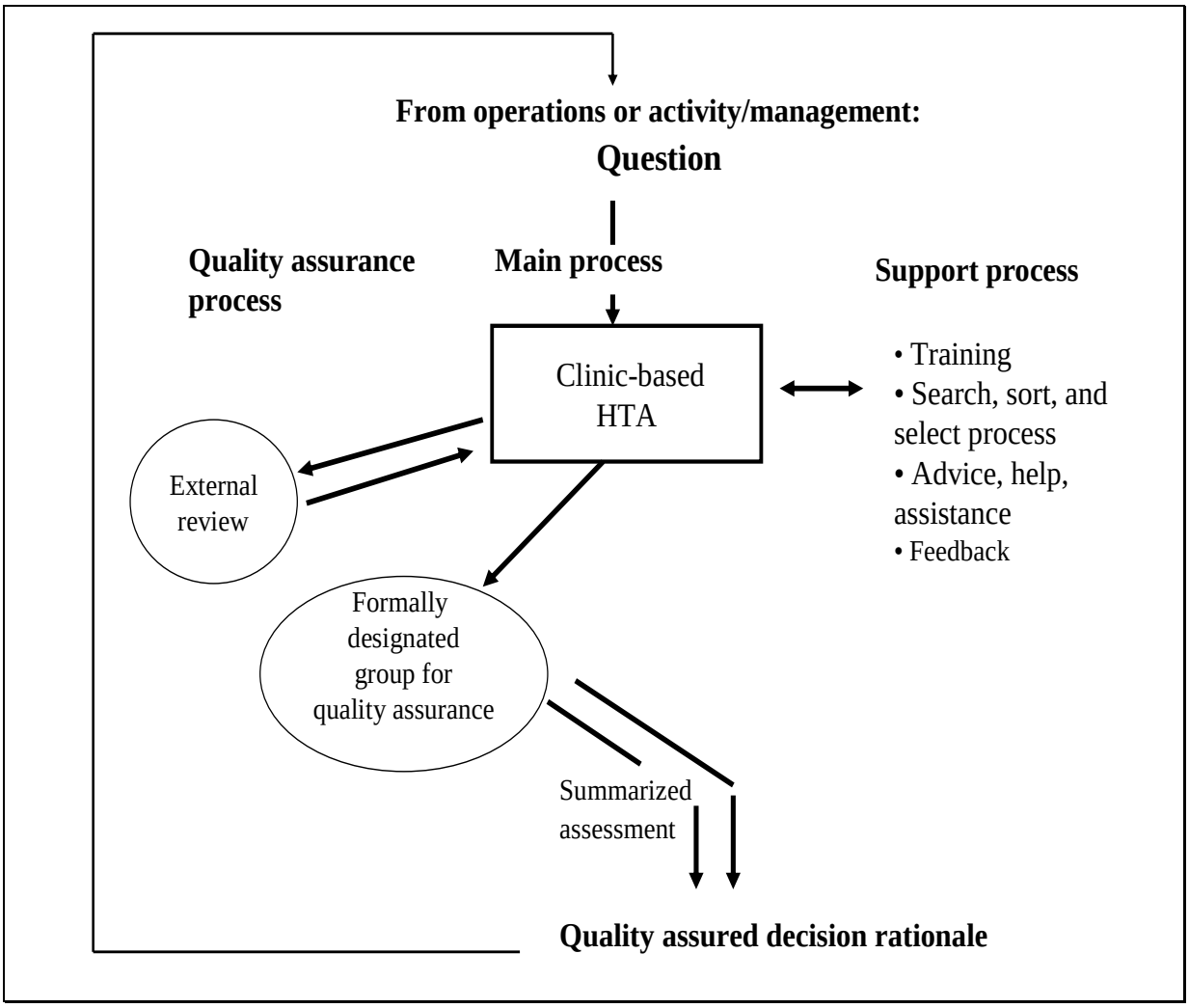
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum