Interventions for great saphenous vein reflux: network meta-analysis of randomized clinical trials

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Abstract

Background: A variety of endovascular and open surgical interventions exist to treat great saphenous vein reflux. However, comparisons of treatment outcomes have been inconsistent.

Methods: A systematic review and network meta-analysis of RCTs was performed to compare rates of incomplete stripping or non-occlusion of the great saphenous vein with or without reflux (anatomical failure) at early, mid- and long-term follow-up; and secondary outcomes (reintervention and clinical recurrence) among intervention groups. The surface under the cumulative ranking curve (SUCRA) method was used to estimate the probability of the intervention with the lowest anatomical failure rates.

Results: Some 72 RCTs were included. Comparisons of endothermal techniques with open surgery were mostly not significantly different, except for endovenous laser ablation (EVLA), which had higher long-term anatomical failure rates (pooled risk ratio (RR) 1.87, 95 per cent c.i. 1.14 to 3.07). Mechanochemical ablation had higher anatomical failure rates than radiofrequency ablation (RFA) (pooled RR 2.77, 1.38 to 5.53), and cyanoacrylate closure (CAC) had a RR 0.56 (0.34 to 0.93) times lower than either RFA or EVLA at the early term. Ultrasound-guided foam sclerotherapy had a higher risk of anatomical failure and reintervention than open surgery, with the lowest SUCRA value, and CAC was ranked first, third and first for best intervention for anatomical failure at early, mid and long term respectively. However, clinical recurrence rates were not significantly different between all comparisons.

Conclusion: Mechanochemical ablation and ultrasound-guided foam sclerotherapy performed poorly, with higher anatomical failure rates in the long term. The other treatment modalities had similar rates of anatomical failure in the short and mid term.

Introduction

Endovenous thermal ablation methods, including radiofrequency ablation (RFA) and endovenous laser ablation (EVLA), have been recommended instead of open surgery for the treatment of great saphenous vein reflux1,2. Other non-invasive modalities are available, including ultrasound-guided foam sclerotherapy (UGFS) and non-thermal non-tumescent (NTNT) techniques, such as mechanochemical ablation (MOCA) and cyanoacrylate closure (CAC).

A meta-analysis3 in 2012 demonstrated similar efficacies in the mid term (1–3 years) for rates of incomplete stripping or non-occlusion of the great saphenous vein (GSV) with or without reflux (anatomical failure) following RFA and EVLA, but poorer outcomes for UGFS, compared with open surgery. However, findings from two recent meta-analyses4,5 of RCTs that assessed long-term outcomes (more than 5 years) reached conflicting conclusions, with one4 reporting similar rates of anatomical failure between open surgery and EVLA, and the other5 demonstrating significantly greater anatomical failure after EVLA at long-term follow-up compared with open surgery.

Previous studies4–5 have focused solely on anatomical failure rates, whereas other important clinical outcomes, including neovascularization and reflux in tributaries (such as anterior accessory saphenous vein (AASV) reflux) that contribute to the efficacy of the procedures, have been considered insufficiently6–8. Furthermore, several studies9–14 have applied combined techniques (high open surgical ligation (HL) with EVLA or UGFS), but these were not pooled separately.
The primary aim of this systematic review and network meta-analysis was to quantify the rates of anatomical failure between the treatment techniques. In addition, a variety of secondary outcomes were assessed.

Methods

The study was conducted according to the PRISMA guidelines \(^{15}\) and extension statement for network meta-analysis of healthcare interventions \(^{16}\). The published protocol was registered at PROSPERO (number CRD42018096794) \(^{17}\).

Search strategy and study selection

MEDLINE and Scopus were searched from 2011 to March 2020. Search terms were based on patients and interventions \(^{17}\). Two reviewers independently selected studies according to predefined inclusion criteria: RCTs of GSV reflux; comparison of defined interventions as outlined below; and reporting any of the primary or secondary outcomes of interest. Data from multiple publications involving the same cohort were combined.

Interventions

Interventions of interest included open surgery, endothermal ablation (EVLA, RFA), UGFS, CAC, and MOCA. In addition, EVLA and UGFS procedures that were combined with HL were also considered.

Outcomes

Anatomical failure (incomplete stripping or GSV non-occlusion with or without reflux, as defined in the original study) \(^{9}\) was regarded as the primary outcome of interest. Secondary outcomes included postoperative complications (wound infection, haematoma, paraesthesia and venous thromboembolism), postoperative pain, time to recovery, Venous Clinical Severity Score (VCSS), AASV reflux, neovascularization, clinical recurrence, reintervention, and quality of life as measured by the Aberdeen Varicose Vein Questionnaire (AVVQ). Outcomes including anatomical failure, neovascularization, AASV reflux, VCSS and AVVQ scores were measured and stratified according to follow-up time as periprocedural (less than 30 days), early term (30 days to 1 year), mid term (1–3 years) and long term (more than 3 years) \(^{4}\).

Data extraction

Data, including characteristics of studies and patients, such as setting, interventions, outcomes, mean age, severity, GSV diameter, co-intervention (compression, concomitant phlebectomy), were extracted independently by two of three reviewers. In addition, data for pooling (frequency data among interventions and dichotomous outcomes; mean(s.d.) values of continuous outcomes by intervention group) were extracted. Corresponding authors were contacted twice to request unreported data for pooling. Discrepancies between reviewers were resolved by consensus.

Risk-of-bias assessment and grading of evidence

The Cochrane Collaboration tool \(^{18}\) was used by two independent reviewers to assess sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome reports, selective outcome reports, and other sources of potential bias. In addition, the quality of evidence was graded using the GRADE working group tool \(^{19}\) to consider study limitations, consistency, indirectness, imprecision and publication bias.

Statistical analysis

Direct meta-analysis was applied for direct comparison of intervention and comparator when at least three studies reported the same comparisons and outcomes. Effect sizes (risk ratio (RR) and risk difference for dichotomous outcomes, mean difference (MD) or standardized mean difference (SMD) for continuous outcomes) with 95 per cent c.i. were estimated. A fixed-effect model was used when effect sizes demonstrated low levels of heterogeneity across studies; otherwise a random-effects model was used. When studies did not report mean(s.d.) values, these were estimated from median (range/i.q.r.) values \(^{20}\). Number needed to treat (NNT) and harm (NNH) along with 95 per cent c.i. were estimated by inverse of pooled risk differences.

The Q test and \( I^2 \) values were used to assess heterogeneity. Outcomes with either a significant Q test results (\( P < 0.100 \)) or \( I^2 \) value of 25 per cent or more were considered heterogeneous \(^{21}\). Possible sources of heterogeneity (such as wavelength and per-protocol analysis) were explored by means of meta-regression. Subgroup or sensitivity analyses were performed accordingly. Publication bias was assessed with Egger’s test and funnel plots. Contour-enhanced funnel plots were assessed to determine whether asymmetry was likely due to heterogeneity or publication bias.

Network meta-analysis \(^{22}\) was performed by borrowing information from the common comparators where direct comparisons were not available to compare outcomes indirectly among interventions (RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, MOCA, CAC and open surgery). Effect sizes and variance–covariance were estimated for individual studies and pooled in a multi-variable consistency model meta-analysis. Mixed intervention comparisons were also estimated. A surface under the cumulative ranking curve (SUCRA) based on the frequentist method was used to estimate the probability of the best intervention. The SUCRA method used cumulative posterior probability with 1000 simulations to estimate the probability of each intervention being the best ranked; values range from 0 to 100 per cent, where the higher value demonstrates high likelihood of being the best intervention.

The inconsistency assumption was tested using a design-by-treatment interaction model; if this was unmet, inconsistency factors were estimated and tested. Comparison-adjusted funnel plots were explored for evidence of small study effects across the whole network. A cluster rank plot of SUCRA for anatomical failure on the y-axis and postoperative pain on the x-axis was constructed \(^{23}\). Analysis was performed using STATA \(^{24}\) version 16.0 (StataCorp, College Station, TX, USA) with a threshold of \( P < 0.050 \) for the two-sided test considered statistically significant \(^{25}\).

Results

Seventy-four RCTs \(^{5,7,9–14,24–89}\) met the study inclusion criteria (Fig. S1). Of them, 26 studies were the same as other RCTs but reported outcomes measured at different times, leaving 48 original RCTs for qualitative and risk-of-bias assessment (Table S1). A total of 49 RCTs \(^{5,7,9–14,24–56,79–87}\) from 30 studies compared endovenous ablation with open surgery, and the remainder included comparisons between endovenous ablation methods only (Table S1). Duration of follow-up ranged from 0.5 months to 8 years, with 18 of the 48 studies (38 per cent) reporting long-term outcomes (more than 3 years). Most studies included participants
with a mean GSV diameter below 10 mm, with the exception of a single study that reported a mean GSV diameter above 10 mm.

**Risk-of-bias assessment**

Results from the risk-of-bias assessment are presented in Table S2. Blinding domains represented the highest risk, with 85 and 75 per cent of RCTs unblinded for personnel and outcome assessors respectively. Approximately 30 per cent of RCTs had randomizations that were unclear or had a high risk of bias. However, most studies (95 per cent) had a low risk of bias for incomplete and selective outcome reports.

**Anatomical failure**

**Direct meta-analysis**

For EVLA versus open surgery, there were between 5 and 12 comparisons of anatomical failure at periprocedural, early, mid-term and long-term follow-up (Table 1). Anatomical failure rates were not significantly different for EVLA in relation to open surgery at periprocedural to mid-term follow-up (Fig. S2). However, anatomical failure at long-term follow-up after EVLA was significantly higher than after surgery, with a pooled RR of 1.87 (95 per cent c.i. 1.14 to 3.07) and NNH of 20 (12 to 59). Sources of heterogeneity (I² = 53.5 per cent) were explored by fitting different types of waveform in a meta-regression and sensitivity analysis with study exclusion according to protocol, however, the source of heterogeneity could not be determined (data not shown). The contour-enhanced funnel plots suggested publication bias at early-term follow-up (Fig. S3).

Comparisons of RFA and open surgery outcomes were reported in five or six RCTs at periprocedural, early, and mid-term follow-up, (Table 1 and Fig. S4). Anatomical failure risk was 1.26 (95 per cent c.i. 0.20 to 7.99), 1.99 (0.92 to 4.31) and 1.45 (0.75 to 2.80) times greater for RFA than for open surgery at periprocedural, early and mid-term follow-up respectively, although none was significant and I² values were 0 per cent for early and mid-term follow-up. Evidence of publication bias was not identified for any pooled comparisons (Fig S4).

Comparisons of UGFS and open surgery outcomes were reported in three to nine RCTs at periprocedural, early, mid-term and long-term follow-up (Fig. S5). The anatomical failure risk was significantly higher at early, mid-term and long-term follow-up with corresponding RRs of 2.47 (95 per cent c.i. 1.78 to 3.43; NNH 6 (4 to 14), 2.14 (1.42 to 3.23; NNH 6 (5 to 10) and 3.06 (1.74 to 5.36; NNH 4 (2 to 9), with moderate to high levels of heterogeneity detected (I² values between 37.3 and 84.5 per cent). Sensitivity analyses through the exclusion of a study that reported combined outcomes of UGFS with HL did not reduce the heterogeneity. Contour-enhanced funnel plots suggested missing studies from mid-term to long-term follow-up (Fig. S6).

The pooling of 10 RCTs of EVLA and RFA outcomes at early term identified significantly lower rates of anatomical failure for EVLA compared with RFA (RR 0.75, 95 per cent c.i. 0.58 to 0.97;

Table 1 Direct meta-analysis of anatomical failure comparison between intervention types

| Comparison arms               | Follow-up time | No. of studies | Intervention type | Events per no. of patients | Pooled RR | NNT/NNH | Heterogeneity | Egger's test | Quality |
|-------------------------------|----------------|----------------|-------------------|----------------------------|------------|---------|---------------|-------------|---------|
| EVLA versus OS                | Periprocedural | 10             | EVLA Surgery      | 14 of 940                  | 0.65 (0.28, 1.52) | –       | 0.193         | 28.1        | 0.077   | High| 3 | 3 | 3 |
| Early                         |                | 12             | EVLA Surgery      | 23 of 865                  | 1.14 (0.84, 1.55) | –       | 0.428         | 1.7         | 0.020   | Moderate| 3 | 3 | 3 |
| Mid term                      | 5              |                | EVLA Surgery      | 77 of 1375                 | 1.24 (0.69, 2.22) | –       | 0.224         | 23.8        | 0.504   | High| 3 | 3 | 3 |
| Long term                     | 9              |                | EVLA Surgery      | 32 of 760                  | 1.18 (1.14, 3.07) | 20 (12, 59) | 0.042         | 53.5        | 0.158   | Moderate| 3 | 3 | 3 |
| RFA versus OS                 | Periprocedural | 6              | RFA Surgery       | 14 of 367                  | 1.26 (0.20, 7.99) | –       | 0.053         | 58.7        | 0.240   | Low| 3 | 3 | 3 |
| Early                         | 6              |                | RFA Surgery       | 10 of 358                  | 1.99 (0.92, 4.31) | –       | 0.617         | 0.653       | 0.328   | Moderate| 3 | 3 | 3 |
| Mid term                      | 5              |                | RFA Surgery       | 17 of 261                  | 1.45 (0.75, 2.80) | –       | 0.653         | 0.032       | 0.328   | Moderate| 3 | 3 | 3 |
| UGFS versus open surgery      | Periprocedural | 5              | UGFS Surgery      | 15 of 376                  | 0.96 (0.51, 1.81) | –       | 0.587         | 0.136       | 0.901   | Moderate| 3 | 3 | 3 |
| Early                         | 9              |                | UGFS Surgery      | 270 of 948                 | 2.47 (1.78, 3.43) | 6 (4, 14) | 0.064         | 37.3        | 0.812   | High| 3 | 3 | 3 |
| Mid term                      | 3              |                | UGFS Surgery      | 122 of 414                 | 2.14 (1.42, 3.23) | 6 (5, 10) | 0.169         | 43.6        | 0.148   | Moderate| 3 | 3 | 3 |
| Long term                     | 6              |                | UGFS Surgery      | 298 of 861                 | 3.06 (1.74, 5.36) | 4 (2, 9) | <0.001        | 84.5        | 0.011   | Low| 3 | 3 | 3 |
| EVLA versus RFA               | Periprocedural | 5              | EVLA RFA          | 3 of 376                   | 1.25 (0.37, 4.26) | –       | 0.984         | 0.877       | 0.664   | Moderate| 3 | 3 | 3 |
| Early                         | 10             |                | EVLA RFA          | 68 of 912                  | 0.75 (0.58, 0.97) | 18 (33, 200) | 0.519         | 0.190       | 0.905   | High| 3 | 3 | 3 |
| Mid term                      | 3              |                | EVLA RFA          | 27 of 419                  | 0.97 (0.50, 1.60) | –       | 0.978         | 0.090       | 0.905   | Low| 3 | 3 | 3 |
| CAC versus endothermal        | Early          | 3              | CAC RFA           | 20 of 483                  | 0.56 (0.34, 0.93) | 30 (17, 200) | 0.364         | 0.165       | 0.905   | Moderate| 3 | 3 | 3 |
| MOCA versus RFA               | Early          | 3              | MOCA RFA          | 49 of 604                  | 2.77 (1.38, 5.53) | 12 (8, 29) | 0.359         | 0.312       | 0.905   | Moderate| 3 | 3 | 3 |

Values in parentheses are 95 per cent confidence intervals. *Early, up to 1 year; mid-term, 1–3 years; long-term, more than 3 years. †Number needed to treat/harm (NNT/NNH) values were estimated only for significant results. RR, risk ratio; EVLA, endovenous laser ablation; OS, open surgery; RFA, radiofrequency ablation; UGFS, ultrasound-guided foam sclerotherapy; CAC, cyanoacrylate closure; MOCA, mechanochemical ablation.
NNT 18 (33 to 200; I²=0 per cent), although there was no significant effect observed at mid term (RR 0.97, 0.59 to 1.60). Evidence of publication bias was not detected (Fig. S7).

Three RCTs compared CAC with endothermal ablation (RFA and EVLA). The risk of anatomical failure was significantly lower after CAC compared with endothermal ablation at early term, with a pooled RR of 0.56 (95 per cent c.i. 0.34 to 0.93) and NNT of 30 (17 to 200). In contrast, the anatomical failure risk at early term was higher after MOCA than RFA (pooled RR 2.77, 1.38 to 5.53; NNH 12, 8 to 29). Both results were homogeneous (I²=0 per cent) with no publication bias (Fig. S8).

**Network meta-analysis**

Network meta-analyses of anatomical failure were generated from 26, 37, 17 and 15 RCTs for periprocedural, early-term, mid-term and long-term outcomes respectively (Table 2 and Fig. S9). The global test indicated consistent results for all networks (Table S3). None of the interventions was significantly different to open surgery at periprocedural follow-up.

Comparisons of open surgery and MOCA showed that MOCA had greater anatomical failure at both early and mid-term follow-up (pooled RR 3.34 (95 per cent c.i. 1.55 to 7.19) and 2.03 (0.69 to 6.01) respectively), but only early term was significant. UGFS had significantly higher anatomical failure than open surgery at early, mid-term and long-term follow-up with pooled RRs of 3.05 (2.41 to 3.86), 2.60 (1.54 to 4.41) and 3.98 (2.18 to 7.28) respectively. All types of endothermal ablation (RFA, EVLA and EVLA with HL) showed no significant differences in anatomical failure compared with open surgery at early and mid term, although EVLA had a significantly higher level of anatomical failure at long-term follow-up (RR 1.90, 1.08 to 3.34).

CAC comparisons with open surgery showed a lower risk of anatomical failure at periprocedural, early and long-term follow-up (RR 0.21 (95 per cent c.i. 0.01 to 6.84), 0.65 (0.36 to 1.17) and 0.62 (0.08 to 4.60) respectively), but none was significant (Table 2). Comparisons of CAC with MOCA and UGFS showed that MOCA had a significantly higher anatomical failure rate than CAC at early term (RR 1.98, 1.17 to 3.35); EVLA and EVLA with HL also had a higher risk than CAC, but this was not significant. MOCA and UGFS had significantly greater risks of anatomical failure compared with CAC, RFA and EVLA at early term (Table 2).

Consideration of the additional effect of HL on anatomical failure identified a significantly higher failure rate following UGFS compared with UGFS with HL at early follow-up (RR 4.28, 95 per cent c.i. 1.30 to 4.73); this was also reflected at mid-term and long-term follow-up, but was not significant (Table 2). EVLA also showed an increased risk of failure between 1.61 and 1.92 times higher than EVLA with HL at both mid-term and long-term follow-up, but neither was significant.

SUCRA values associated with the lowest risk of anatomical failure were calculated for each follow-up period (Table S4). CAC was the top ranked intervention in lowering anatomical failure risk at the periprocedural, early and long-term follow-up. Open surgery and endothermal ablation were largely ranked next, followed by MOCA and UGFS with HL, whereas UGFS alone was

| Table 2 Network meta-analysis risk ratios of anatomical failure between intervention type and time of follow-up |
|---------------------------------------------------------------|
| **Early term** | **Mid term** | **Long term** |
| **Open surgery** | 1.62 (0.32, 8.27) | 1.30 (0.49, 4.34) | 2.03 (0.43, 9.58) |
| **MOCA** | 1.01 (0.54, 1.90) | 1.92 (1.57, 2.32) | 0.72 (0.32, 1.63) |
| **CAC** | 0.93 (0.37, 2.44) | 2.48 (2.09, 3.04) | 0.70 (0.24, 2.05) |
| **UGFS with HL** | 1.09 (0.37, 3.14) | 2.54 (2.10, 3.09) | 0.75 (0.28, 2.37) |
| **EVLA with HL** | 0.81 (0.15, 4.18) | 0.63 (0.32, 1.25) | 1.07 (0.31, 3.70) |
| **RFA** | 0.62 (0.39, 0.97) | 2.05 (1.54, 2.71) | 0.58 (0.24, 1.32) |
| **RFA** | 0.59 (0.36, 0.99) | 2.56 (1.97, 3.34) | 0.58 (0.24, 1.32) |
| **UGFS** | 0.86 (0.54, 1.40) | 1.42 (0.97, 2.14) | 0.56 (0.28, 1.00) |
| **EVLA** | 0.09 (0.04, 0.22) | 2.71 (1.17, 6.22) | 0.37 (0.15, 0.87) |

Values in cells are risk ratios (95 per cent c.i.) of anatomical failure, comparing the intervention in the diagonal line with the side relative to the intervention on the left side. For instance, the risk ratio for endovenous laser ablation (EVLA) versus open surgery is 0.63 (95 per cent c.i. 0.27 to 1.48) and 1.00 (0.74 to 1.34) at periprocedural and early follow-up times respectively: MOCA, mechaanochemical ablation; CAC, cyanoacrylate closure; UGFS, ultrasound-guided foam sclerotherapy; HL, high ligation; RFA, radiofrequency ablation.
Table 3 Direct meta-analysis comparisons of secondary outcomes between intervention types and time of follow-up

| Comparison arm | Outcomes                   | Follow-up time | No. of studies | Events per no. of patients | Pooled RR or MD | NNT/NNH* | Heterogeneity | Egger’s test | Quality |
|---------------|---------------------------|----------------|----------------|----------------------------|-----------------|---------|---------------|-------------|---------|
| EVLA versus OS | Neovascularization        | Early term     | 4              | 0 of 371                   | 0.06 (0.01, 0.28) | 16      | 0.639         | 0           | 0.256   | Moderate |
|               |                           | Mid term       | 3              | 0 of 385                   | 0.03 (0.01, 0.18) | 9       | 0.370         | 0           | 0.207   | Moderate |
|               |                           | Long term      | 8              | 25 of 766                  | 0.38 (0.20, 0.74) | 11      | 0.061         | 40.8        | 0.018   | Moderate |
|               | AASV reflux               | Long term      | 7              | 77 of 674                  | 3.62 (2.31, 5.67) | 15      | 0.462         | 1.6         | 0.185   | High    |
|               | Clinical recurrence       | End of follow-up | 7             | 217 of 937                | 0.91 (2.31, 5.67) | 11      | 0.038         | 56.4        | 0.573   | Low     |
|               | Reintervention            | End of follow-up | 9             | 99 of 784                  | 0.92 (0.70, 1.17) | –       | 0.635         | 0           | 0.293   | High    |
|               | VCSS†                     | Early term     | 6              | –                          | 0.00 (0.00)       | –       | 0.991         | 0           | 0.653   | High    |
|               |                           | Mid term       | 4              | –                          | -0.01 (0.00)      | –       | 0.737         | 0           | 0.438   | High    |
|               |                           | Long term      | 4              | –                          | -0.08 (0.00)      | –       | <0.001        | 90.6        | 0.029   | High    |
|               | AVVQ†                     | Early term     | 7              | –                          | -0.74 (0.19)      | –       | 0.010         | 65.3        | 0.583   | Moderate |
|               |                           | Mid term       | 6              | –                          | 0.36 (0.13, 0.59) | –       | 0.671         | 0           | 0.772   | High    |
|               |                           | Long term      | 6              | –                          | 0.16 (0.02, 0.3)  | –       | 0.005         | 73.7        | 0.285   | Moderate |
| RFA versus OS | Neovascularization        | Mid term       | 3              | 2 of 79                    | 0.45 (0.13, 1.54) | –       | 0.672         | 0           | 0.632   | Moderate |
|               | Clinical recurrence       | End of follow-up | 5             | 43 of 324                  | 0.81 (0.46, 1.45) | –       | 0.145         | 42.9        | 0.322   | Moderate |
| UGFS versus OS | Reintervention            | End of follow-up | 7             | 223 of 943                 | 1.79 (1.41, 2.27) | 2       | 0.104         | 34.0        | 0.620   | High    |
|               | VCSS†                     | Early term     | 3              | –                          | 0.13 (0.01, 0.27) | –       | 0.001         | 89.9        | 0.901   | Moderate |
|               | AVVQ†                     | Early term     | 4              | –                          | -0.73 (0.98)      | –       | 0.007         | 80.8        | 0.283   | Moderate |

Values in parentheses are 95 per cent confidence intervals. *Number need to treat (NNT) was estimated only for significant results. †Continuous outcomes. RR, risk ratio; MD, mean difference; NNT, number needed to harm; EVLA, endovenous laser ablation; OS, open surgery; AASV, anterior accessory saphenous vein; VCSS, Venous Clinical Severity Score; AVVQ, Aberdeen Varicose Vein Questionnaire; RFA, radiofrequency ablation; UGFS, ultrasound-guided foam sclerotherapy.

Secondary outcomes

Secondary outcomes, including neovascularization, AASV reflux, clinical recurrence and reintervention, were considered (Table 3). Results demonstrated consistently lower neovascularization following EVLA compared with open surgery at early, mid-term and long-term follow-up (pooled RR 0.06 (95 per cent c.i. 0.01 to 0.28), NNT 16 (8 to 250); 0.03 (0.01 to 0.18), NNT 9 (7 to 13); and 0.38 (0.20 to 0.74), NNT 11 (6 to 48) respectively). There was no evidence of heterogeneity, except for long-term follow-up (pooled RR 0.20 (0.09 to 0.47) respectively) (Table 3 and Fig. S12). Reintervention was significantly greater after UGFS compared with open surgery (RR 1.79 (1.41 to 2.27); NNT 2 (1 to 3)) (Fig. S12). Similarly, VCSS and AVVQ showed no significant differences at early, mid-term and long-term follow-up for EVLA comparisons with open surgery, and at early follow-up for UGFS versus open surgery (Figs S13-S15).

Postoperative complications were also assessed (Table 4). Venous thromboembolism was not significantly different for any comparison. EVLA, RFA and UGFS were significantly less likely to be associated with wound infection than open surgery (RR 0.41 (95 per cent c.i. 0.21 to 0.79), 0.25 (0.07 to 0.89) and 0.48 (0.25 to 0.95) respectively), with low to moderate levels of heterogeneity. In addition, EVLA, RFA and UGFS had a significantly lower risk of haematoma than open surgery (RR 0.55 (0.33 to 0.93), 0.29 (0.11 to 0.74) and 0.36 (0.23 to 0.56) respectively). Paraesthesia was significantly reduced following EVLA and UGFS compared with open surgery (RR 0.64 (0.46 to 0.89) and 0.20 (0.09 to 0.47) respectively). Paraesthesia was also significantly lower for NTNT treatments relative to endothermal ablation (RR 0.35 (0.14 to 0.85)). Furthermore, superficial thrombophlebitis was significantly greater in RFA and UGFS treatments compared with open surgery (RR 2.63 (1.34 to 5.14) and 3.41 (1.36 to 8.59) respectively).
For postoperative pain after endothermal ablation and open surgery, RFA resulted in significantly less pain than open surgery (pooled MD $-1.3$, 95 per cent c.i. $-1.6$ to $-0.9$, $I^2=0$ per cent) and EVLA (pooled MD $-0.98$, $-1.55$ to $-0.40$, $I^2=95.8$ per cent) (Table 5). A subgroup analysis by wavelength (less than 1470 versus 1470 nm) reduced the $I^2$ value from 95.8 to 0 per cent for RFA versus EVLA comparisons. For studies with a wavelength below 1470 nm, RFA involved significantly less pain than EVLA (pooled MD $-1.44$, $-1.66$ to $-1.22$) than those with a wavelength of 1470 nm, where RFA had significantly greater pain than EVLA (pooled MD $0.20$, 0.09 to 0.31) (Fig. S16).

There was no significant difference in postoperative pain between MOCA and endothermal ablation (either RFA<sup>66,68</sup>, RFA and 1470-nm EVLA<sup>69</sup>, or 1470-nm EVLA<sup>69</sup>) with a pooled MD of $-0.26$ (95 per cent c.i. $-1.29$ to 0.76, $I^2=91.2$ per cent) (Table 5 and Fig. S17). However, CAC had lower postoperative pain than endothermal ablation (SMD $-1.37$, $-1.98$ to $-0.75$), with high heterogeneity.

A network meta-analysis of postoperative pain showed consistent trend results between direct and network meta-analyses (Tables S3 and S5). Ranking indicated that CAC was the most effective method in lowering postoperative pain in the x-axis (Fig. 1). The plot was divided into four quadrants at the SUCRA value of 0.5: interventions that fell in the right upper and lower quadrant had low pain
with low and high anatomical failure respectively, whereas those in the left upper and lower quadrants had high pain with low and high anatomical failure. Therefore, the best intervention should fall in the right upper quadrant, with values for CAC indicating low anatomical failure and low postoperative pain for both mid-term and long-term follow-up.

EVLA, RFA and UGFS were associated with 3–4 and 4–8 days shorter return to normal activities and work compared with open surgery, with high levels of heterogeneity. NTNT had significantly reduced time to normal activities compared with endothermal ablation (pooled MD −0.9, 95 per cent c.i. −1.5 to −0.3; I² = 92 per cent), but this was not significantly different for time to work.

Quality of evidence
The quality of the body of evidence for direct meta-analysis was graded according to each outcome across studies (Tables S6–S9). The most common reason for a reduction in the quality of evidence was serious imprecision as a result of inadequate sample size.

Discussion
This study failed to identify any significant differences in anatomical failure from comparisons between open surgery and RFA and EVLA at early and mid-term follow-up. The network meta-analysis did, however, identify significantly higher levels of anatomical failure with EVLA at long-term follow-up, although no data were available for assessment of RFA in the longer term. At early-term follow-up, CAC resulted in lower levels of anatomical failure than endothermal ablation, supported by a moderate quality of evidence. MOCA was associated with higher levels of anatomical failure compared with RFA, with a NNH value of 12 (95 per cent c.i. 8 to 29). Network meta-analysis also showed higher levels of anatomical failure following MOCA compared with open surgery, CAC, RFA, UGFS with HL, and EVLA at early follow-up. UGFS was associated with a higher risk of anatomical failure than open surgery in both direct and network meta-analyses, with NNH values ranging between 2 and 14 across all periods of follow-up with the lowest SUCRA value.

The data also demonstrated greater anatomical failure for EVLA at long-term follow-up compared with open surgery, with findings of moderate quality due to heterogeneity. These findings contrast with the previous meta-analysis, which found no evidence of difference in anatomical failure rates between EVLA and open surgery. However, the present study supports the conclusions from the meta-analysis by Kheirelseid and colleagues, which reported significantly greater GSV recanalization following EVLA compared with open surgery, with a pooled RR of 2.28 (95 per cent c.i. 1.20 to 4.30).

In early-term follow-up, direct meta-analysis identified reduced anatomical failure after CAC compared with endothermal ablation, with moderate levels of quality associated with imprecision (the upper boundary of NNT was as high as 200 and with a suboptimal sample size). In addition, CAC ranked better than RFA for having the lowest anatomical failure rate in the network meta-analysis, scoring first, third and first rank for early, mid-term and long-term follow-up respectively. The findings of this study are consistent with a recent network meta-analysis of
group analysis by wavelength reduced the blood within, could reduce pain and complications. The sub-length EVLA (1470 nm), which targets the vein wall instead of explained within the analysis. Variation from lower to higher wave explained through variation in the wavelength of EVLA consid- effect observed failed to reach significance. This may be the benefits of EVLA relative to open surgery were reduced, the lowing RFA and UGFS compared with open surgery. Although ablation in terms of postoperative pain and recovery time fol- 1.54).

were not significantly different (RR 0.99 (95 per cent c.i. 0.63 to perficial thrombophlebitis with endothermal ablation and NTNT were not significantly different across the rate of GSV recanalization following CAC (8.6 per cent) and RFA (14.8 per cent)\(^7\). AASV reflux was significantly greater following EVLA, whereas neovascularization was greater after open surgery, with little differ- in NNT/NNH values. However, anatomical failure, AASV reflux and neovascularization were surrogate outcomes of clinical recur- rence that were not significantly different in the present analyses. In addition, other important patient outcomes, such as VCSS, AVVQ scores and reintervention, were also not significantly different be- yond the higher reintervention rate observed after UGFS in relation to open surgery, although these outcomes should be considered further. Other likely sources of recurrence include perforator insufficiency, saphenopopliteal reflux and primary varicosities, which should be considered across different types of intervention. More detailed clas- sification of clinical recurrence associated with specific interventions would facilitate comparisons of efficacies between interventions. Paraesthesia was reduced after NTNT compared with endo- thermal ablation, which may result from lower levels of thermal injury to the adjacent nerve during the procedure, whereas superficial thrombophlebitis was not significantly different across the comparisons assessed. Postprocedure phlebitis was the most common complication following CAC\(^8\), and comparisons of superficial thrombophlebitis with endothermal ablation and NTNT were not significantly different (RR 0.99 (95 per cent c.i. 0.63 to 1.54).

The data in this study confirmed the benefit of endovenous ablation in terms of postoperative pain and recovery time fol- lowing RFA and UGFS compared with open surgery. Although the benefits of EVLA relative to open surgery were reduced, the effect observed failed to reach significance. This may be explained through variation in the wavelength of EVLA consid- ered within the analysis. Variation from lower to higher wave- length EVLA (1470 nm), which targets the vein wall instead of blood within, could reduce pain and complications. The sub- group analysis by wavelength reduced the \(i^2\) value to zero, resulting in significantly higher pain recorded at wavelength thresholds below 1470 nm and lower pain levels at thresholds of 1470 nm for EVLA comparisons with RFA. Two RCTs\(^9\,\(^{10}\) also reported significantly lower levels of pain and complications at EVLA wavelengths of 1470 nm.

CAC was also associated with lower postoperative pain com- pared with endothermal ablation, possibly as a consequence of non-thermal mechanisms of ablation or perhaps due to unneces- sary use of tumescent anaesthesia. Although MOCA does not need tumescent anaesthesia, its mechanical injury of vein during the procedure may cause discomfort. The quality of evidence was graded as moderate, owing to inconsistency\(^7\,\(^{10}\).

The efficacies, benefits and harms, together with measures on the quality of evidence according to outcomes, were reported in the pre- sent study to support physician decisions when choosing the most appropriate intervention for individual patients. For instance, if anatomi- cal failure is the main concern in the mid and long term, open surgery might be best, given its associated complications are similar to those of other techniques. If patient outcome such as postopera- tive pain is of more concern, CAC might be preferred over open sur- gery and other interventions, given that anatomical failure is not much different to that for open surgery. However, this should be interpreted with caution because data for other important outcomes (neovascularization, AASV reflux, clinical recurrence and quality of life) were not available for CAC comparisons.

There are some limitations to this study. Although comparis- ons of many relevant clinical outcomes were included, important patient outcomes such as symptomatic improvement were not considered owing to lack of available data. Quality of life, mea- sured by the AVVQ, was available for a small number of studies of endothermal ablation, but not for CAC or MOCA. Cost is also an impor-tant consideration, but was not part of the present analysis.

**Supplementary material**

Supplementary material is available at BJS online.

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