Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Nonthermal Endovenous Procedures for Varicose Veins: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Varicose veins are enlarged, twisted veins that are visible under the skin, often in the legs. They are a sign that the veins do not move blood effectively back to the heart. People with varicose veins may experience aching, burning, swelling, skin colour changes, or more severe complications including bleeding and open wounds (venous ulcers).

In those with significant symptoms, surgery to remove the problem veins has been the traditional treatment. Newer, less invasive procedures use either laser or radiofrequency heat inside the veins (endovenous) to burn them closed. Thermal endovenous procedures can be done in a doctor's office instead of an operating room, but they still require a type of local anesthesia. There is interest in nonthermal (not heat-based) endovenous alternatives. The nonthermal endovenous methods are called cyanoacrylate adhesive closure (CAC), which uses a medical glue to close varicose veins, and mechanochemical ablation (MOCA), which uses a combination of physical and chemical methods to close the problem veins.

This health technology assessment looked at how safe, effective, and cost-effective nonthermal endovenous procedures are for people with symptomatic varicose veins. It also looked at the budget impact of publicly funding thermal and nonthermal endovenous procedures and at the experiences, preferences, and values of people with varicose veins.

What Did This Health Technology Assessment Find?

People whose varicose veins were treated with MOCA had poorer vein closure, but similar improvement in symptoms and quality of life as the thermal endovenous procedures. Those treated with CAC had similar success in vein closure, improved symptoms, and quality of life as people who were treated with thermal endovenous procedures. Recovery times after both nonthermal endovenous procedures were slightly shorter than for all other procedures. The effectiveness of CAC compared with vein surgery is very uncertain. Complications were similar between treatments, and major adverse events were rare.

Compared with vein surgery, all endovenous treatments were more cost-effective. If thermal and nonthermal endovenous treatments are publicly funded in Ontario for adults with symptomatic varicose veins, the potential target population could increase considerably. Assuming an 80% increase in the number of eligible people, we estimate the total 5-year budget impact would be around $17 million.

In interviews, patients reported on the negative impact of living with varicose veins and on their health care journey to seek treatment. People only had experience with cyanoacrylate adhesive closure and reported positive experiences with the procedure and said it resolved their symptoms and improved their quality of life.

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Abstract

Background

Varicose veins are part of the spectrum of chronic venous disease and are a sign of underlying chronic venous insufficiency. Treatments to address varicose veins include surgical vein removal under general anesthesia, or endovenous laser (EVLA) or radiofrequency ablation (RFA) under tumescent anesthesia. Two newer nonthermal endovenous procedures can close veins without any tumescent anesthesia, using either mechanochemical ablation (MOCA, a combination of mechanical and chemical techniques) or cyanoacrylate adhesive closure (CAC). We conducted a health technology assessment of these nonthermal endovenous procedures for people with symptomatic varicose veins, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding MOCA and CAC, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane Risk of Bias or RoBANS tool, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. Meta-analysis was conducted using Review Manager 5.2, where appropriate.

We performed a systematic economic literature search and conducted a cost–utility analysis with a 5-year time horizon from the perspective of Ontario Ministry of Health. In our primary economic evaluation, we assessed the cost-effectiveness of nonthermal endovenous procedures (CAC and MOCA) compared with surgical vein stripping and thermal endovenous therapies (EVLA and RFA). We also analyzed the budget impact of publicly funding nonthermal and thermal endovenous therapies for adults with symptomatic varicose veins in Ontario over the next 5 years. Costs are expressed in 2020 Canadian dollars.

To contextualize the potential value of nonthermal endovenous treatments, we spoke with 13 people with varicose veins who had sought various treatment options. We conducted phone interviews and qualitatively analyzed their responses regarding their care journey and the impact of different treatment options; the only nonthermal treatment that participants had experience with was CAC.

Results

We included 19 primary studies reported in 25 publications comparing either MOCA or CAC with at least one other invasive treatment for symptomatic varicose veins. No studies compared MOCA with CAC. Based on evidence of low to moderate quality, MOCA resulted in slightly poorer technical outcomes (vein closure and recanalization) than thermal endovenous ablation procedures. However, clinical outcomes, quality of life improvement, and patient satisfaction were similar compared with RFA (GRADE: Very low to Moderate) and EVLA (GRADE: High). Cyanoacrylate adhesive closure resulted in little to no difference in technical outcomes, clinical outcomes, and quality of life improvement compared with RFA and EVLA (GRADE: Moderate). Patient satisfaction may also be similar (GRADE: Low). Recovery time was slightly reduced with nonthermal endovenous procedures compared with thermal ablation (GRADE: Moderate). The effect of CAC compared with surgical vein stripping is very uncertain (GRADE: Very low). Major complications of any procedure were rare, with minor complications occurring as expected and resolving.

We included two European studies in the economic evidence review that were partially applicable to the Ontario context. Both studies found that thermal ablation procedures (RFA, EVLA, or steam vein sclerosis) were the most cost-effective treatments, compared with surgical vein stripping and nonthermal therapies. Our cost–utility analysis showed that surgical vein stripping is the least effective and most costly treatment among five treatments for varicose veins. Differences in quality-adjusted life-years (QALYs) between endovenous treatments (CAC, MOCA, RFA, and EVLA) were small. When the willingness-to-pay (WTP) value was $50,000 per QALY gained, the probabilities of being cost-effective were 55.6%, 18.8%, 15.6%, 10.0%, and 0%, for EVLA, CAC, MOCA, RFA, and surgical vein stripping, respectively. When the WTP was $100,000 per QALY gained, the probabilities of being cost-effective were 40.2%, 30.0%, 17.7%, 12.1%, and 0%, for EVLA, CAC, RFA, MOCA, and surgical vein stripping, respectively. Publicly funding endovenous procedures (both nonthermal and thermal) would increase the total volume of treatments, resulting in a total 5-year budget impact of around $17 million.

People with varicose veins with whom we spoke reported positively on their experiences with the CAC procedure and its outcomes. They also described geographic and financial barriers to accessing the range of available treatment options

Conclusions

Cyanoacrylate adhesive closure and MOCA produced similar patient-important outcomes, and slightly shorter recovery compared with thermal ablation. Cyanoacrylate adhesive closure yielded similar anatomical outcomes as thermal endovenous ablation, but the technical outcomes of MOCA were slightly poorer.

Compared with surgical vein stripping, all endovenous treatments were more effective and less expensive. If we were to look at the most cost-effective strategy (at WTP less than $100,000 per QALY), EVLA is most likely to be cost-effective. Assuming an 80% increase in the number of eligible people over the next 5 years, we estimate that publicly funding nonthermal and thermal endovenous treatments for varicose veins in Ontario would range from $2.59 million in year 1 to $4.35 million in year 5, and that the total 5-year budget impact would be around $17 million.

For people with varicose veins, the CAC procedure was seen as a positive treatment method that reduced their symptoms and improved their quality of life.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of nonthermal endovenous procedures (i.e., mechanochemical ablation [MOCA] and cyanoacrylate adhesive closure [CAC]) for people with symptomatic varicose veins. It also evaluates the budget impact of publicly funding nonthermal endovenous procedures and the experiences, preferences, and values of people with chronic venous disease.

Background

Health Condition

Varicose veins are part of the spectrum of chronic venous disease and are a sign of underlying venous insufficiency, a condition in which blood is not circulated effectively back to the heart.[1,2] Varicose veins in the lower extremities (legs and feet) are enlarged, dilated, and tortuous (twisted) veins that are prominent and visible, appearing as bulging purple or blue-green protrusions under the skin.[2] They usually develop because of malfunctioning valves (valvular incompetence), leading to inefficient pumping of blood back to the heart, reverse blood flow (reflux), and increased blood pressure in the vein.[1,2] Any vein where blood pressure increases may become varicose, and among the commonly affected veins are the superficial veins in the legs, which lie above the muscle and below the skin. These include the great saphenous vein (GSV) and small saphenous vein (SSV) (collectively referred to as the truncal veins) and their tributaries.

Many people with varicose veins have no symptoms. Over time, varicose veins may lead to localized symptoms around the vein (aching, throbbing, itching) or more advanced symptoms of fatigue, heaviness, and cramps in the legs.[1-3] Chronic venous insufficiency (CVI) may progress to more advanced venous disease, including edema (swelling), permanent discolouration of the skin, eczema (inflamed, itchy skin), lipodermatosclerosis (hardening of the skin and the fat layer below it), and venous ulcers (open wounds).[3] According to one estimate, up to 10% of adults with varicose veins will develop advanced venous disease, including venous ulcers,[3,4] superficial thrombophlebitis (inflammation that leads to blood clots), or bleeding from the varicosities. The progression of CVI is not linear, and the timing to or likelihood of advanced venous disease varies among individuals.[5]

Diagnosing and assessing the severity of varicose veins typically includes a clinical interview, physical examination, and duplex ultrasonography (imaging to look at the speed of blood flow and structure of the leg veins) to confirm venous reflux.[6] Venous disease severity is characterized according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification (Table 1).[7] According to the CEAP classification, clinical manifestations level C2 through C6 can represent true varicose veins, with or without observable complications and symptoms.[7] All clinical classes are further specified as either symptomatic or asymptomatic.[8] Asymptomatic varicose veins are considered a cosmetic issue.

Table 1: Chronic Venous Disease Severity According to the CEAP Classification System

Severity	Description
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias (spider veins) or reticular veins (< 2 mm diameter)
C_2	Varicose veins (> 3 mm diameter)
C_3	Edema relating to venous insufficiency
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis (colour and texture skin changes) or atrophie blanche (white skin scarring)
C_5	Healed venous ulcer
C_6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps and other complaints attributable to venous dysfunction
A	Asymptomatic

Abbreviations: CEAP, Clinical-Etiology-Anatomy-Pathophysiology.
Source: Eklof et al, 2004.[7]

Clinical Need and Target Population

Risk factors for developing varicose veins include both modifiable (e.g., lack of exercise, smoking, obesity, prolonged standing or sitting) and nonmodifiable factors (e.g., age, family history, deep vein thrombosis, tall height).[3] Genetics are the most important factor in varicose vein development, with a 25% to 62% increased risk if one parent has varicose veins and a 90% increased risk if both parents have them.[9] Female sex slightly increases the risk of developing varicose veins because of the physiological and hormonal effects of pregnancy and overall elevated estrogen levels compared with male sex.[3]

Approximately 80% to 85% of adults will have some form of chronic venous disease, including telangiectasias (spider veins), reticular veins (slightly larger blue-purple veins), and varicose veins.[3] The prevalence of true varicose veins ranges in the literature, most commonly around 20% to 30%[3,10-12] up to as much as 65% of adults.[13] The annual incidence of varicose veins estimated from the Framingham Study (a large, long-term, ongoing cardiovascular cohort study) was reported to be 2.6% among females and 1.9% among males.[14] Epidemiological studies estimated that, of the general population presenting with symptomatic varicose veins, about 14% had varicose veins alone (i.e., CEAP class C2) and about 17% presented with more advanced clinical stages of venous insufficiency (i.e., CEAP class C3 to C6).[8] A study of primary care patients with symptomatic varicose veins found the distribution of these CEAP classes to be around 21% and 10%, respectively.[15] In an international study of symptomatic varicose vein cases in primary care and specialist practices, about 35% of patients had CEAP 2 varicose veins alone and the remaining 65% had more advanced venous disease (CEAP 3+ i.e., edema, skin changes, healed venous ulcer, or active venous ulcer).[16]

The symptoms of varicose veins and venous disease negatively affect a person's quality of life.[8] The largest quality of life decrement tends to be in people with active or healed venous ulcers.[16] It is well established that venous leg ulcers are challenging and persistent,[17] significantly reduce people's quality of life,[9,18] and are costly to the health care system.[19] In addition, bleeding events from varicose veins can

be associated with frequent emergency department visits, especially for older patients. Regardless of CEAP severity class, physical and mental health-related quality of life in people with symptomatic varicose veins is significantly reduced.[20] Effective treatment of varicose veins can alleviate symptoms and improve health-related quality of life.[21] The magnitude of this improvement has been documented as comparable to the improvement in health-related quality of life after gallbladder surgery to treat a gallbladder attack (gallstones).[22] In a condition like chronic venous insufficiency, where mortality is low, quality of life is arguably the most important outcome measure for people with symptomatic varicose veins.[20]

In addition to impacts on quality of life, there may be an association between varicose veins and important venous events. Research within the past decade has found an elevated incidence of potentially life-threatening deep vein thrombosis (a blood clot blocking blood flow in the deep veins) and pulmonary embolism (a blockage to a lung artery, usually due to a blood clot) in people with varicose veins.[23,24] Some research also suggests an association between varicose veins and the risk of developing peripheral artery disease.[23,24] However, the relationship between arterial and venous disease is not well understood as their risk factors and treatments differ.

Terminology

In this report, we use *invasive* to mean any procedure that aims to resolve venous insufficiency by removing or closing incompetent veins. These procedures can involve open surgical approach, incisions, or punctures and may use various types of anesthesia to gain access to the vein for treatment. Some treatments are considerably less invasive than others.

We use *surgical vein stripping* to refer to any vein-removal surgery, with or without ligation or phlebectomy. When we are reporting on a study that has specified surgical details, we use the terminology of the study (e.g., high ligation and stripping; high ligation is the tying off of the femoral vein at the top of the thigh).

And we use *technical outcomes* or *technical success* to refer to whether a procedure has achieved a desired anatomical change. For example, varicose vein closure (as seen on duplex ultrasound) is often monitored in studies of endovenous procedures. Vein closure is an important technical outcome of the intervention and might influence the likelihood of requiring reintervention. However, vein closure does not necessarily reflect changes in patient-important outcomes (such as clinical symptoms or quality of life), which tend to improve after treatment even with imperfect technical outcomes.

Current Treatment Options

Broadly speaking, four treatment options are available for people with varicose veins: no intervention (if veins are asymptomatic), compression therapy, surgery, and endovenous ablation.

Compression therapy, the conservative therapy for symptomatic varicose veins, uses prescription compression stockings or bandages with medical-grade pressure gradients (i.e., > 20 mmHg).[25] Compression therapy does not address the underlying issue of venous reflux, but aims to manage symptoms such as pain and swelling.[26] In advanced venous disease (i.e., venous ulcers), compression can facilitate healing and can be used alone or in conjunction with invasive treatments.[27]

To treat superficial venous insufficiency, the incompetent (malfunctioning) veins must be either closed or removed, and the body reroutes the circulation of blood to the deep venous system via perforator

veins. Traditional surgical vein stripping of symptomatic varicose veins involves physical removal of the diseased veins.[28] The surgery targets the saphenous veins as the primary site of venous reflux with ligation (tying off the vein) at the saphenofemoral junction (in the upper thigh) and stripping of the great saphenous vein (GSV), along with phlebectomy (removal) of the vein's small tributaries through 2-mm incisions. Vein surgery is performed as day surgery in a hospital operating room, typically under general, spinal, or epidural anesthesia. In extremely rare cases, patients may require a brief hospitalization. Recovery from surgery takes typically 2 to 3 weeks to return to normal activities, including work.[17] Recurrence of venous insufficiency (in new veins) after surgical vein stripping is around 10% to 20%.[29]

Advances in technology have led to the emergence of minimally invasive techniques for endovenous ablation ("within the vein"). These include endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), both of which employ specialized equipment and catheters, with thermal energy (heat) delivered through either a laser fibre or radiofrequency catheter, respectively. The objective of the treatment is ablation (destruction) of a refluxing vein or segment of vein.[30] The treated vein and associated tributaries subsequently close or collapse, leaving only fibrotic remnants (scar tissue) that fade into adjacent tissue. Both procedures require the use of ultrasound guidance and are performed using tumescent anesthesia (a large volume of dilute local anesthetic is infused under the skin along the length of the vein to numb and firm up the area for treatment). In contrast to surgical vein stripping, RFA and EVLA are performed in a clinic setting and do not require an operating room.[17,31] Both procedures have been found to be less invasive, safe, and cost-effective alternatives to surgical vein stripping.[30] Table 2 summarizes surgical stripping and the thermal endovenous treatment options.

Sclerotherapy is a medical procedure that may be used to supplement surgery or endovenous treatments for varicose veins. Sclerotherapy involves injecting a solution directly into a small tributary vein, which causes the vein to scar and close, forcing blood to reroute through competent veins. Liquid or foam sclerotherapy, with or without ultrasound guidance, can also be used on the tributaries of the varicose veins as adjunctive therapy after primary treatment (clinical experts, telephone communication, November 1–8, 2019).

Table 2: Overview of Invasive Treatments for Symptomatic Varicose Veins

	Procedure		
	Surgical Vein Stripping	**RFA**	**EVLA**
Anatomic indications	Low to high vein tortuosity	GSV diameter > 3 mm Low vein tortuosity	GSV diameter > 3 mm Low vein tortuosity
Location	Operating room	Clinic	Clinic
Professionals	Vascular or general surgeon	Any physician trained in endovenous procedures[a]	Any physician trained in endovenous procedures[a]
Anesthesia	General, spinal, or epidural	Local tumescent	Local tumescent
Additional varicosities treated	At same time	Typically, subsequent sclerotherapy injections	Typically, subsequent sclerotherapy injections
Recovery time	2–3 weeks	< 1 week	< 1 week
Therapeutic mechanism	Vein removal	Vein closure	Vein closure

Abbreviations: EVLA, endovenous laser ablation; GSV, great saphenous vein; RFA, radiofrequency ablation.
[a]Any physician with expertise in ultrasound-guided vascular access and basic catheter and wire skills can theoretically perform endovenous procedures. Typically performed by vascular or general surgeons, or interventional radiologists.
Sources: Medical Advisory Secretariat, 2010[31]; Medical Advisory Secretariat, 2011.[17]

The profile of potential complications for each procedure tends to be mostly minor, though differs somewhat in nature. For instance, paresthesia (tingling or pricking sensations) and thrombophlebitis are more common minor complications with EVLA and less common with RFA, whereas ecchymosis (bruising) is more common with RFA.[28] Skin burns after EVLA are not very common. Complications of surgical vein stripping occur in less than 5% to 20% of patients.[17] Nerve injury and sensory loss are more common minor complications after surgical vein stripping, while major complications such as hematomas (pooling of blood under the skin), lymph leaks, pulmonary embolism, femoral vein and artery injury, or deep vein thrombosis are very rare.[28]

For people with symptomatic varicose veins, any of the treatment options described above may be appropriate, depending on an individual's condition (e.g., nature of underlying venous incompetence, tortuosity of the vein, presence of scar tissue inside veins from prior blood clots). Diameter of the great saphenous vein has also been associated with disease severity (CEAP classification) and, potentially, treatment outcomes.[32] Guidelines, including the National Institute for Health and Care Excellence,[5] American College of Phlebology,[26] and the Society for Vascular Surgery and the American Venous Forum[28] (which the Canadian Society for Vascular Surgery follows), recommend surgery for people whose condition is not appropriate for endovenous thermal procedures.

Health Technologies Under Review

Two newer, nonthermal endovenous technologies have become popular in the landscape of treatment for symptomatic varicose veins: MOCA and CAC. These procedures are nonthermal techniques (i.e., they do not rely on heat) to close the saphenous veins. These procedures may be preferred over thermal ablation for the below-knee segment of the GSV and for treatment of the SSV because they minimize

the possibility of nerve damage compared with EVLA or RFA (clinical expert, email communication, January 8, 2020).

Mechanochemical ablation is a procedure involving the use of a special catheter that combines two modalities of treatment for varicose veins: endovenous mechanical vein destruction with a rotating wire and the simultaneous infusion of a liquid sclerosant (chemical irritant that causes inflammation) to enhance venous occlusion (closure of the vein).[11] The approach involves the use of ultrasound guidance to position and move the catheter. This technique ablates veins without tumescent anesthesia; the veins scar and are sealed.[11] There is one commercially available MOCA device on the market used most widely, called ClariVein (Merit Medical Systems, USA).

Cyanoacrylate adhesive closure uses ultrasound guidance to position a catheter and deliver a measured dose of cyanoacrylate glue to seal the vein.[33] The catheter is withdrawn in stages and pressure is applied to the leg (externally) to glue the vein closed. Cyanoacrylate adhesive closure aims to close varicose veins first by adherence, and then by fibrosis (scarring) of the vein lumen (interior walls), without the need for any anesthesia.[33] Over time, the body replaces the adhesive with scar tissue that keeps the vein closed. However, because the adhesive remains in the body for a period of time after the procedure, up to 5% of people receiving the procedure may experience hypersensitivity or allergic or foreign body reactions (clinical experts, telephone communications, October 2019 to January 2020). Severe hypersensitivity reactions tend to be very rare (< 0.5%), with most cases that do occur being mild and self-limited.[34] Three similar CAC devices are on the market: VenaSeal (Medtronic, USA), VariClose (Biolas, Turkey), and VenaBLOCK (Invamed, Turkey).

Regulatory Information

Both nonthermal endovenous technologies are approved by Health Canada and hold active medical device licences. The ClariVein system has been licensed since 2010 as a Class II medical device (License No. 83246) and is indicated for endovascular occlusion of incompetent veins in patients with superficial venous reflux (Health Canada, email communication, November 22, 2019). VenaSeal has been licensed as a Class III device since 2013 (License No. 83246), with indications “for the permanent, complete, endovascular adhesive closure of the GSV and associated varicosities” (Health Canada, email communication, November 22, 2019). VariClose and VenaBLOCK do not currently hold Health Canada licenses. The US Food and Drug Administration has approved both VenaSeal and ClariVein for use in the United States.[35]

Ontario, Canadian, and International Context

Neither MOCA nor CAC are currently publicly funded in Ontario. To our knowledge, most private insurance plans also do not cover these procedures. To receive these treatments, patients must pay out-of-pocket at a private clinic, at a cost on the order of $2,500 to $4,500 per leg, depending on their chosen procedure and the clinic (clinical experts, telephone communications, October 25 to November 14, 2019).

The Ontario Health Insurance Plan (OHIP) currently requires conservative management of varicose veins prior to more invasive procedures. OHIP only provides coverage for surgical stripping and sclerotherapy to treat varicose veins in the GSV and/or SSV meeting all criteria: venous incompetence at the saphenofemoral or saphenopopliteal junction documented by ultrasonography, a failed trial of compression therapy for at least 3 months, in addition to one or more listed signs of advanced chronic venous insufficiency (i.e., eczema, pigmentation, lipodermatosclerosis, ulceration) or listed

complications (see Schedule of Benefits for full list).[36] Medical-grade compression stockings are not publicly funded for most patients, although the Ontario Health Technology Advisory Committee (OHTAC) recommended public funding of compression therapy in 2019[19] for people with healed venous ulcers (e.g., C5 venous disease). According to local experts, the OHIP funding criteria for varicose vein surgery are not clearly linked to clinical evidence. Surgery needs to be done in an operating room, where allocated time is very limited.

In 2010 and 2011, Health Quality Ontario (formerly the Medical Advisory Secretariat and now a part of Ontario Health) assessed the clinical and cost-effectiveness of EVLA and RFA for treatment of symptomatic varicose veins, and OHTAC made its recommendation on those procedures in 2013.[17,30,31] The recommendation was that both thermal endovenous therapies should be made available to people with symptomatic varicose veins and saphenous venous reflux demonstrated on a full duplex ultrasound investigation and, when feasible, following a failed trial of conservative management.[30] However, there is no public funding or fee code in the Schedule of Benefits for minimally invasive procedures for varicose veins, including endovenous laser therapy and radiofrequency ablation. Most patients must pay out-of-pocket at private clinics for EVLA or RFA treatment, which ranges in cost from approximately $2,500 to $5,500 depending on the practitioner and complexity of the venous problem (clinical experts, telephone and email communications, October 2019 to January 2020). Thermal endovenous ablation is also not an insured service anywhere in Canada except in two health regions in Saskatchewan that have introduced publicly funded RFA and EVLA by reallocating internal funds (email communication, October 28, 2020).

To our knowledge at the time of writing, no Canadian province or territory provides public funding for either MOCA or CAC. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends the use of MOCA (IPG557, May 2016)[11] and CAC (IPG670, March 2020)[37] as treatment options provided by qualified professionals based on adequate effectiveness and safety data. The Medical Services Advisory Committee in Australia reviewed the available evidence and recommended public coverage of CAC for treatment of small and great saphenous veins, with fees set to be identical to fees for RFA and EVLA (July 2017).[38]

Equity Considerations

According to local clinical experts, the primary equity issue affecting treatment for varicose veins in Ontario is access, owing to several factors: (i) surgical vein stripping is the only publicly funded procedure and is restricted to cases meeting OHIP criteria[36]; (ii) access to publicly funded surgery for eligible people may be limited to specific centres or days when operating room time is allocated for surgical vein stripping; (iii) all endovenous procedures must be paid for out-of-pocket and private insurance covers only a small number of cases in part or whole; thus access is restricted to people who can afford it. People whose access to surgical vein stripping is limited by geographical or health system constraints could be treated for venous insufficiency if clinic-based endovenous procedures were funded. Elderly patients with limited financial means and greater comorbidity (e.g., with an ulcer or bleeding event) are most significantly disadvantaged as they may be neither a candidate for surgery nor able to afford noninsured endovenous ablation. Ontario clinical experts stress that public funding of treatments for varicose veins should be based on medical need, as opposed to being restricted to one of many effective treatments.

Expert Consultation

We engaged with experts in the specialty areas of general and vascular surgery, interventional radiology, and family medicine, and with stakeholders who provide strategic leadership on vascular care in Ontario to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence. We also engaged with relevant manufacturers or distributors to obtain technical and financial information about the devices.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42020166940), available at https://www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the clinical effectiveness and safety of mechanochemical ablation (MOCA) and cyanoacrylate adhesive closure (CAC) compared with other invasive procedures for people with symptomatic varicose veins?

Methods

Clinical Literature Search

We performed a clinical literature search on January 14, 2020, to retrieve studies published from January 1, 2012, until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHSEED). We chose 2012 as a starting point because, although ClariVein obtained CE mark in 2010, the first in-human study of this MOCA device was published in 2012 and, of the two technologies being reviewed, it was developed first.[39]

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[40]

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period (until September 15, 2020). We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2012, and January 14, 2020
- Systematic reviews that include comparative studies, or comparative studies (randomized controlled trials [RCTs], nonrandomized studies)
    - Reviews must clearly report search methods (e.g., keywords, dates) and include at least one known medical database

Exclusion Criteria

- Noncomparative studies
- Studies of multiple interventions where results for MOCA or CAC cannot be separated
- Editorials, commentaries, case reports, conferences abstracts, letters
- Unpublished or draft data or manuscripts
- Animal and in vitro studies

Preference was given to systematic reviews, and, if included, we planned to assess risk of bias using the Risk of Bias in Systematic Reviews (ROBIS) tool.[41] We aimed to select a systematic review(s) that matched our PICO (participants, interventions, comparators, and outcomes) and was of highest methodological quality with consideration to lowest risk of bias, recency, and comprehensiveness. If no systematic review was available or of adequate quality or recency to answer the research question, we included and analyzed primary studies.

PARTICIPANTS

We included studies of adults (age 18 years and older) with symptomatic varicose veins or more advanced venous disease in the great and/or small saphenous veins of the legs (i.e., CEAP classification C2,S–C6 inclusive, see Table 1 for details).

INTERVENTIONS

We included studies comparing CAC (VenaSeal, VenaBLOCK, VariClose or other commercially available device) and/or MOCA (ClariVein or other commercially available device) on the great or small saphenous veins with each other or any of:

- Thermal endovenous ablation (laser [EVLA] or radiofrequency [RFA])
- Surgery (surgical vein stripping [with or without ligation] or phlebectomy, either alone or in combination)
- Saphenous vein–preserving endovenous interventions (such as CHIVA or ASVAL; see Glossary), or
- Sclerotherapy (liquid or foam, with or without ultrasound guidance) on the great or small saphenous veins

Experimental procedures or devices not commercially available were excluded.

OUTCOME MEASURES

- Vein closure (excluding vein removal surgeries)
- Procedure failure
- Vein recanalization (excluding vein removal surgeries)
- Venous ulcer healing or recurrence
- Major and minor complications
- Change in clinical symptoms (assessed by Venous Clinical Severity Score, CEAP clinical class, or other validated scale)
- Quality of life assessed by a validated generic (e.g., Short Form 36) or disease-specific instrument (e.g., Aberdeen Varicose Vein Questionnaire; Chronic Venous Insufficiency Questionnaire)
- Patient satisfaction
- Recovery time/time off work

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence systematic review software[42] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. We emailed authors of forthcoming publications registered in PROSPERO, clinical trials registries, and conference abstracts, seeking full-text publications.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

In cases where multiple publications reported on the same study, we extracted data primarily from the most recent and comprehensive publication and referred to others to supplement the results (e.g., previous follow-up time points) or methodological information, as necessary.

Where point estimates or related essential data (e.g., interquartile range [IQR], standard deviation [SD], range) were reported graphically only and clearly visible in figures, we approximated values using WebPlotDigitizer software.[43]

Statistical Analysis

Proportions and numbers of events were calculated from reported data where clear outcome definitions, numerators, and denominators were available. We calculated risk ratios for frequent events and odds ratios for infrequent events, along with 95% confidence intervals (CI). Where data were available and pooling was appropriate based on minimal methodological heterogeneity (e.g., study design, follow-up time point), statistical heterogeneity, or clinical diversity (e.g., disease severity, vein diameter), we generated pooled summary estimates using random effects models in Review Manager.[44-46] For recanalization we calculated odds ratios, and for vein closure we calculated risk ratios. In addition, risk differences were calculated to complement the relative effects for these outcomes. Where pooling of data was not appropriate, we present the data in figure or tabular format and provide narrative analysis.

Of the pre-planned subgroup analyses, only the analysis of people with CEAP class C5 or C6 venous disease was possible owing to a lack of discrete data on three other subgroups: patients with bleeding varicosities, those with C2 to C4 disease alone, or patients not fit for surgery. We also separately present the findings on the subpopulation of people with chronic venous insufficiency (CVI) of the small saphenous vein (SSV) alone.

Further, we sought to assess potential equity issues in the effect of nonthermal endovenous treatments in varicose veins across different populations defined by the PROGRESS-Plus categories, a health equity framework recommended by the Campbell and Cochrane Equity Methods Group.[47] This included place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital, plus other key characteristics that stratify health opportunities and outcomes. We were not able to assess the impact of these characteristics because only a single study reported ethnicity of participants.[48]

Critical Appraisal of Evidence

We assessed the risk of bias of each included study using the Cochrane Risk of Bias Tool for randomized trials[49] and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) for nonrandomized studies[50] (Appendix 2).

We evaluated the quality of the body of evidence for comparative outcomes according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[51] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence. Quality of evidence was evaluated by comparison of the nonthermal technology of interest with RFA, EVLA, or multiple interventions. Given the irregularity of reporting complications across studies, including a lack of formal comparisons between interventions, we did not GRADE the evidence on complications.

Results

Clinical Literature Search

The database search of the clinical literature yielded 902 citations published between January 1, 2012, and January 14, 2020. We identified 21 additional citations from searching the grey literature. Seven studies (three systematic reviews, two primary studies, and two updated articles on a primary study) were identified through database alerts during the assessment period. We included 12 systematic reviews[10,13,52-61] and 19 primary studies (reported in 25 articles).[48,62-83] See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

As defined a priori, preference was first given to systematic reviews. Appendix 4, Table A13 presents characteristics of the 12 systematic reviews we identified.[10,13,52-61] Upon examination, the recent systematic reviews did not compare discrete procedures: they either compared one against all others together, or they grouped all procedures together or by classification (e.g., thermal or nonthermal) in the analysis. Several systematic reviews included noncomparative studies in addition to comparative studies. However, all systematic reviews included only studies published up to mid-2019.

Among the systematic reviews were two network meta-analyses (NMAs),[13,61] which provided multiple treatment comparisons between all interventions and simultaneous comparisons of the various competing treatments for chronic venous insufficiency. These NMAs made indirect comparisons of CAC or MOCA with surgical vein stripping. To our knowledge, there are few head-to-head trials and no randomized controlled trials comparing nonthermal endovenous procedures with vein surgery, likely owing to the almost complete replacement of surgical vein stripping by thermal endovenous interventions in the past decade.

The identified systematic reviews offered one or more of the comparisons of interest (i.e., either CAC or MOCA compared with another treatment). However, not all our outcomes were available for the comparisons of interest (Table A13). Given that none of the systematic reviews directly answered our research question, and that we identified nine recently published studies not captured in any published systematic review, we analyzed primary studies.

We included 19 primary studies reported in 25 publications comparing either MOCA or CAC to at least one other procedure for symptomatic varicose veins.[48,62-83] No studies were identified that compared MOCA with CAC.

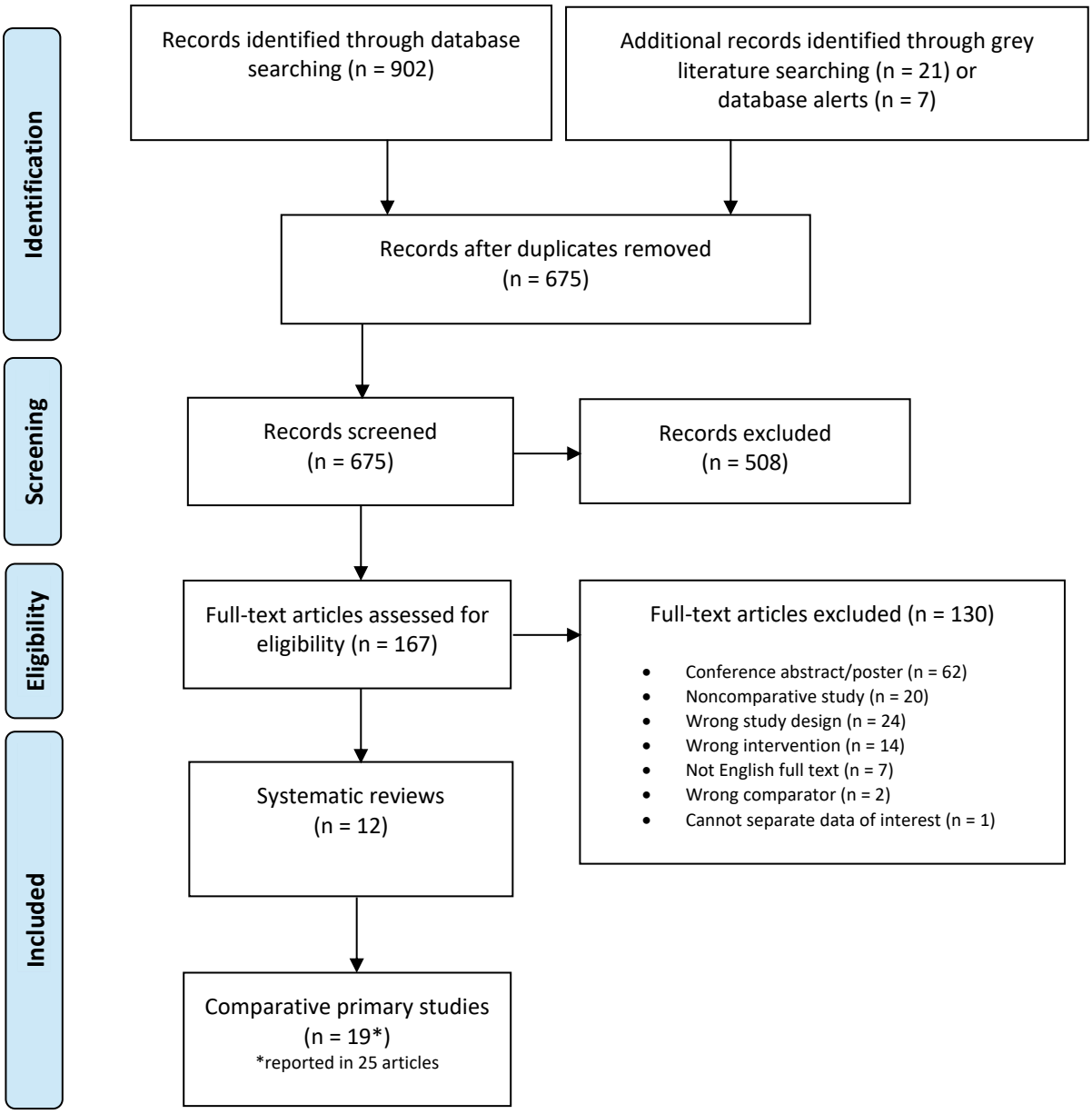

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Source: Adapted from Moher et al, 2009.[84]

Mechanochemical Ablation

Characteristics of Included Studies

Eight studies (four RCTs[74,79,80,83] and four nonrandomized studies,[75-78] reported in 10 publications) compared MOCA (ClariVein device) with either RFA or EVLA (Table 3). Three studies were from the United Kingdom,[74,77,83] two from the Netherlands,[75,79] and one each from the United States,[78] Finland,[80] and Australia.[76]

The characteristics of the included MOCA studies are in Table 3. The studies included patients with various severities of venous insufficiency: many of the study populations had mixed severity of venous disease, predominantly but not exclusively C2 to C4 severity, except for the study by Kim et al 2019,[78] which only examined C6 disease. The great saphenous vein (GSV) was the most common target of treatment, with diameter of the veins generally less than a mean or median of 10 mm. Mean ages of study participants were comparable between groups and generally around 50 years; in the study by Kim et al[78] the patients who received MOCA were significantly older than those receiving thermal ablation (67.9 vs. 57.2 years, P = .0003).

Risk of Bias in the Included Studies

Among the RCTs, only one was judged to be at low risk of bias[83] (Appendix 2, Table A1). The other three had some concerns; the first were related to selective outcome reporting.[80,85] There were also some concerns about risk of bias in another RCT, by Holewijn et al,[79] owing to notable deviation from the planned analysis as per the trial protocol; the trial stopped early due to lack of funding for MOCA, thus did not continue for the planned 2 years and enrolled less than half of planned participants based on sample size calculation. The fourth RCT[74] was judged to have some concerns with potential bias introduced by deviations from the intended interventions and selective outcome reporting. There was not much information provided about the planned statistical analyses, blinding of outcome assessment, and so on. Therefore, it was unclear if the analyses were appropriate or not, or may have altered the results.

Among nonrandomized studies, two were judged to be at unclear risk of bias on one dimension: confounding variables[77] or blinding of outcome assessments[75] (Appendix 2, Table A3). The risk of bias due to confounding variables was judged to be unclear study by Vun et al,[76] while the risk of bias due to incomplete outcome data was judged to be high.[76] The study by Kim et al[78] was judged to be at low risk of bias on all dimensions. [78]

Table 3: Characteristics of Included Studies—Mechanochemical Ablation

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, n (%)		Age, Mean (SD), Y	
			MOCA	Comparator	MOCA	Comparator	MOCA	Comparator
Compared With RFA and EVLA								
Kim et al, 2019[78]	Retrospective chart analysis (United States)	GSV, SSV, ASV, Giacomini, perforator, multiple segments: NR	53[a]	25[b] (thermal treatments combined)	C6 only	C6 only	67.9 (11.6)[c]	57.2 (13.5)[c]
Vahaaho et al, 2019, 2020[80,85]	RCT (Finland)	Thigh GSV *MOCA* 6.7 (1.6) *EVLA* 6.5 (1.6) *RFA* 6.4 (1.8)	59	*EVLA* 34 *RFA* 32	C2: 32 (54.3) C3: 14 (23.7) C4: 13 (22.0) Missing: 0	*EVLA* C2: 20 (58.8) C3: 6 (17.6) C4:7 (20.6) Missing: 1 (2.9) *RFA* C2: 18 (56.2) C3: 7 (21.9) C4:7 (21.9) Missing: 0	50.9 (12)	*EVLA* 49.5 (11.9) *RFA* 50.3 (13.9)
Vun et al, 2015[76]	Prospective cohort (Australia)	GSV, SSV Overall MD 9 (IQR 4–12)	55	*RFA* 50 *EVLA* 40	Overall C2–6		Overall MD 50 (IQR 31–82)	
Compared With EVLA								
Mohamed et al, 2020[83]	RCT (United Kingdom)	GSV, SSV, AASV *MOCA* 6.5 (± 1.5) *EVLA* 6.9 (± 2.1)	75	75	C2: 28 C3: 31 C4: 35 C5: 4 C6: 1	C2: 20 C3: 39 C4: 33 C5: 8 C6: 0	53 (14)	51 (14)

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, n (%)		Age, Mean (SD), Y	
			MOCA	Comparator	MOCA	Comparator	MOCA	Comparator
Compared With RFA								
Holewijn et al, 2019[79]	RCT (Netherlands)	GSV *MOCA* MD 6 (IQR 0.8–12) *RFA* 6 (IQR 1.2–14)	105	104	C2: 5.9 C3: 59.8 C4a: 31.4 C4b: 2 C5: 2	C2: 4.2 C3: 66.7 C4a: 22.9 C4b: 3.1 C5: 3.1	MD 54.9 (IQR 16.3–81.2)	MD 53.4 (IQR 22.8–77.9)
Moon et al, 2017[77]	Prospective cohort (United Kingdom)	GSV: NR	11	17	NR[d]	NR[d]	46 (NR)	55 (NR)
Lane et al, 2017[74]; Bootun et al, 2016[73]	RCT (United Kingdom)	GSV, SSV *MOCA* MD 7 *RFA* MD 7	87	83	MD 4	MD 4	MD 54.5	MD 48
van Eekeren et al, 2013[75]	Prospective comparative cohort (Netherlands)	GSV *MOCA* 5.7 (1.6) *RFA* 6.8 (2.4)[e]	34	34	C1: 3 C2: 47 C3: 23.5 C4: 23.5 C5-6: 3	C1: 0 C2: 26 C3: 30 C4: 41 C5-6: 3	57.2 (15.2)	58 (17.8)

Abbreviations: AASV, anterior accessory saphenous vein; ASV, accessory saphenous vein; CEAP, Clinical-Etiologic-Anatomic-Pathophysiologic classification; CVI, chronic venous insufficiency; EVLA, endovenous laser ablation; GSV, great saphenous vein; IQR, interquartile range; MA, meta-analysis; MD, median; MOCA, mechanochemical ablation; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation; SD, standard deviation; SSV, small saphenous vein; Y, years.

[a]Results reported for 41 in the MOCA group.[78]

[b]As reported by Table 1 in Kim et al, 2019.[78] Article text reports that 11 people underwent EVLA and 18 RFA.

[c]MOCA group significantly older (P = .0003).[78]

[d]Study only reports mean VCSS score of 5.5 in MOCA group, 4.9 in RFA group (P = .6262).[77]

[e]Vein diameter in RFA group was statistically significantly wider (P = .03).[75]

Vein Closure

Vein closure is a technical outcome in the treatment of varicose veins, an anatomical marker of procedural success. Patients receive imaging via duplex ultrasound at various time points after the procedure, to confirm the vein is no longer patent (open).

MOCA VERSUS EVLA, RFA, OR BOTH

Five studies reported on vein closure after mechanochemical ablation compared with either RFA,[79] EVLA,[74,83] or both (Table 4).[76,80] Time points at which vein closure was measured varied from around 1 month to 3 years post-procedure.

Table 4: Vein Closure After Mechanochemical Ablation vs. Thermal Endovenous Ablation

Author, Year (Study Design)	Follow-Up Time Point	Vein Closure, % (n/N)			*P* Value
		MOCA	EVLA	RFA	
Mohamed et al, 2020[83] (RCT)	12 mo	77 (53/69)	91 (63/69)	—	.020
Vahaaho et al, 2019,[80] 2020 (RCT)	12 mo	82 (45/55)	100 (33/33)	100 (29/29)	< .05
	36 mo	80[a] (40/50)	100 (31/31)	100 (25/25)	< .01
Holewijn et al, 2019[79] (RCT)	30 d	91.3 (94/103)	—	99.0 (102/103)	.045
	12 mo	83.5 (66/81)[b]		94.2 (67/72)[b]	.025
	24 mo	80.0 (55/76)		88 (69/81)[b]	.066
Lane et al, 2017; Bootun et al, 2016[73,74] (RCT)	1 mo	93[c,d] (64/69)[b]	—	92[c,d] (55/60)[b]	.403
	6 mo	87[c] (54/62)[b]		93[c] (55/59)[b]	.483
Vun et al, 2015[76] (prospective cohort)	4–6 wk[e]	91% (50/55)	93%[f] (NR)	93%[f] (NR)	NR

Abbreviations: d, day; EVLA, endovenous laser ablation; mo, month; MOCA, mechanochemical ablation; n, number of people; N, total number of people in group; NR, not reported; RFA, radiofrequency ablation; wk, week.

[a]Excludes 1 person who had MOCA and then developed recanalization that was re-treated with EVLA and had complete occlusion.

[b]Calculated from data presented in publication.

[c]Includes both complete occlusion and partial occlusion (defined as > 5 cm proximally occluded, > 5 cm open distally).[74]

[d]Data presented are from Lane et al.[74] 1-month data presented in Table 4 in Bootun et al[73] show 83% complete closure in MOCA group and 92% complete closure in RFA group; however, results reported in the text of the same article[74] and in Lane et al[74] differ.[73]

[e]Study reports duplex ultrasound done 4–6 weeks after procedure.[76]

[f]For EVLA and RFA, this study only reported proportion, citing another study for the proportion of technical success.[76]

Across studies and time points, a greater proportion of veins tended to be successfully closed in the thermal ablation groups (EVLA or RFA) than in the MOCA group (Table 4). This difference of proportions was statistically significant in most comparisons reporting *P* values ($P < .05$). The proportion of people with vein closure in Vun et al[76] were numerically similar, but between-groups differences were not tested statistically.

The differences in proportions of patients with vein closure after MOCA was not significantly different from patients who received EVLA in the study by Lane et al[74] (Table 4). However, unlike all other studies, Lane et al[74] categorized vein closure to include both complete occlusion and proximal occlusion only (see footnote c in Table 4).[74] This different outcome definition may contribute to the differing results.

We rated the quality of the evidence for vein closure compared with RFA as moderate, rating down for risk of bias (Appendix 2, Table A6), and low compared with EVLA, downgrading for risk of bias and imprecision (Appendix 2, Table A5).

As illustrated in Figures 2 and 3, the likelihood of vein closure was lower in the MOCA group compared thermal ablation in nearly all scenarios. The pooled risk ratio for 12 months after the procedure was that vein closure was 15% less likely (95% confidence interval [CI] 7%–22%) after MOCA versus RFA. The pooled absolute difference in vein closure at 12 months was of similar magnitude (see Appendix 4, Figure A1)

The risk ratio from the meta-analysis of MOCA versus EVLA at 12 months showed vein closure was 17% less likely (95% CI 8%–25%). The pooled absolute difference in vein closure was similar (see Appendix 4, Figure A2).

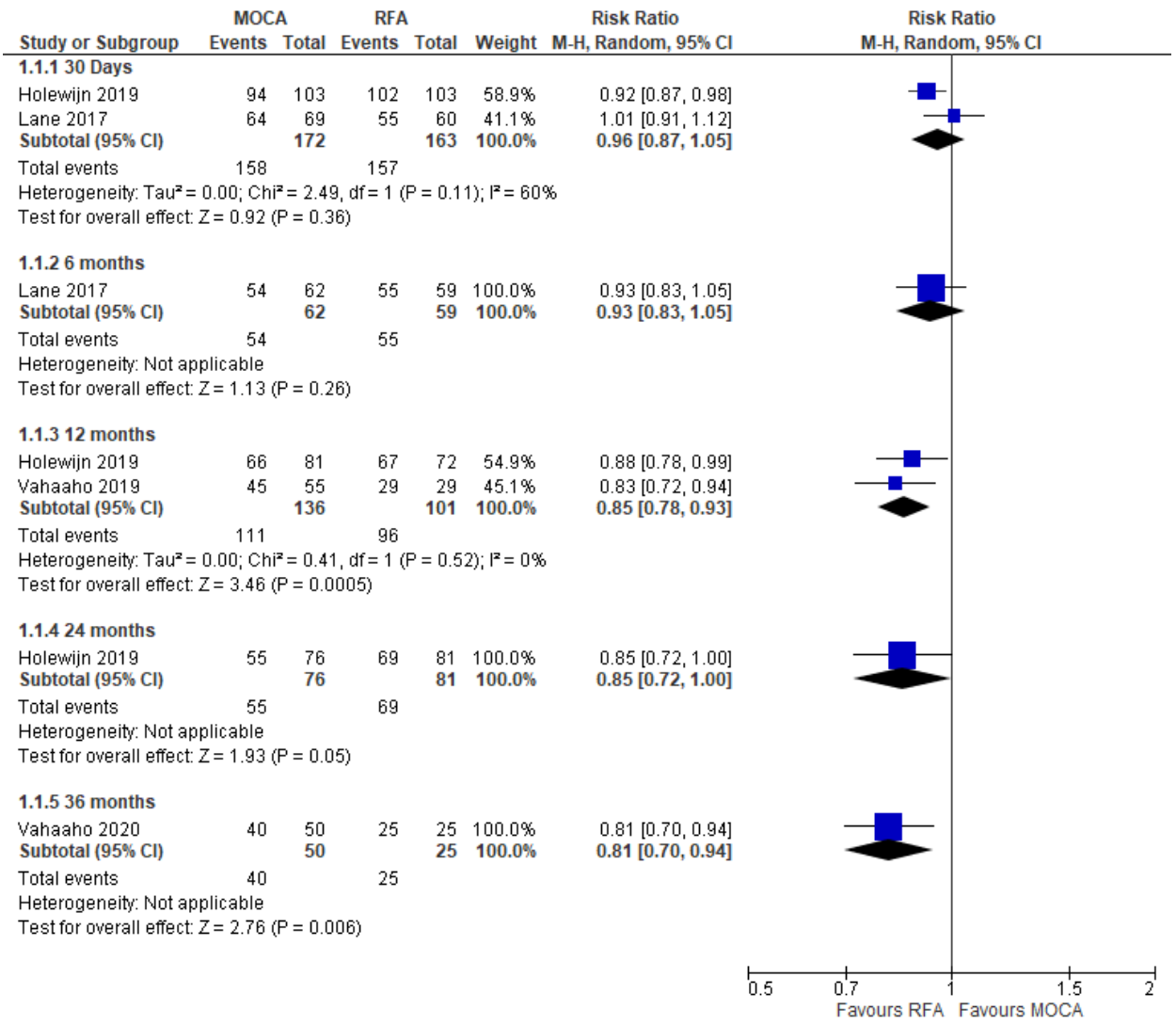

Figure 2: Vein Closure in Randomized Controlled Trials Comparing Mechanochemical Ablation and Radiofrequency Ablation

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MOCA, mechanochemical ablation; RFA, radiofrequency ablation. Event is total vein closure, except for Lane et al[74] which includes both complete and proximal vein closure only (see our Table 4, footnote c). A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the populations in the studies by Holewijn et al[79] and Vahaaho et al.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Holewijn et al, 2019[79]; Lane et al, 2017[74]; Vahaaho et al, 2019.[80]

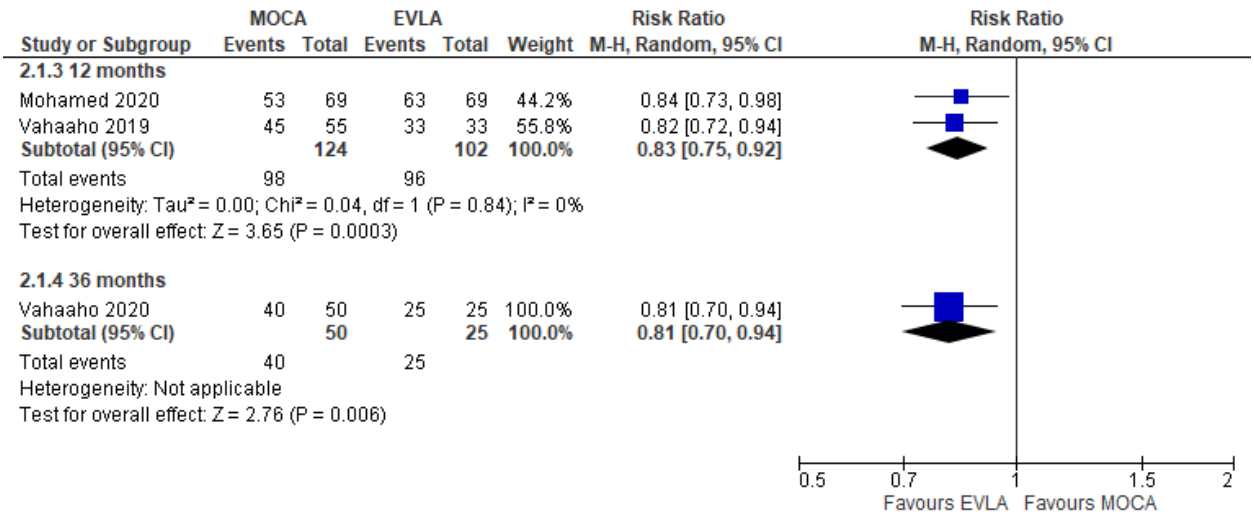

Figure 3: Vein Closure in Randomized Controlled Trials Comparing Mechanochemical Ablation and Endovenous Laser Ablation

Abbreviations: CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel; MOCA, mechanochemical ablation.

Event is total vein closure. A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the trials by Mohamed et al[83] and Vahaaho et al.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Mohamed et al, 2020[83]; Vahaaho et al, 2019.[80]

Procedure Failure and Recanalization

Procedure failure may occur at the time of intervention, due to technical or other issues. Recanalization refers to a vein that has reopened after closure, as detected by duplex ultrasound, and may be partial or complete, with or without detectable blood flow or venous reflux. Recanalization does not necessarily correlate with poor clinical outcomes, quality of life, or lead to reintervention. Four studies reported on occurrences of procedure failure, vein recanalization, and retreatment after MOCA or thermal endovenous procedures (Table 5).[76,79,80,83]

One study compared MOCA to EVLA[83] and one to RFA,[79] and both reported relatively low rates of immediate procedure failure for MOCA (0 and 0.9%, respectively). Mohamed et al[83] reported more complete and partial recanalization in the MOCA group (1% complete, 12% partial recanalization with reflux, 10% partial recanalization without reflux) compared with EVLA (4% complete recanalization above the knee and 1% distal recanalization with reflux). Proportionally, reintervention was performed on 2.7% (or 1 person) in each group.[83] Holewijn et al[79] reported that median time to recanalization in the MOCA group was 12.8 months (range 10–13.7) versus 15.8 months for RFA (range 11.9–24.1).[79] No difference was reported in length or percentage of recanalization of the treated vein segment. Anatomic failure was defined in this study as partial or complete recanalization.[79] There was more recanalization in MOCA at 1- and 2-year follow-up compared with RFA (P = .025), driven mainly by partial recanalization, most commonly in the proximal segment.[79] The proportion of people undergoing reintervention over the 2-year study period is shown in Table 5.

Two other studies[76,80] compared MOCA to both thermal endovenous procedures and reported no recanalization in either thermal ablation group[80] or only reported data on recanalization in the MOCA group[76] (Table 5). Vahaaho et al, 2020[85] reported that, at 3-year follow-up, some of the instances of partial GSV recanalization observed in the MOCA group at 1 year led to complete recanalization at 3 years. Vahaaho et al[80] also noted a strong association between preoperative diameter of the GSV and odds of recanalization; the mean diameter of GSV in patients who experienced recanalization at 1 year was 8.6 mm on average, compared with those who had vein occlusion at 1 year (mean 6.5 mm vein diameter; odds ratio [OR] 0.31, 95% CI 0.13–0.75, $P = 0.009$).[80] In this study, the increased odds of recanalization for greater preoperative vein diameter were even greater at 3-year follow-up (OR 2.15, 95% CI 1.15–4.00, $P = .016$).[85]

The odds of recanalization (partial or complete) after treatment with MOCA tended to be higher than after treatment with either RFA (Figures 4a and 4b) or EVLA (Figures 5a and 5b). Compared with RFA, the odds of recanalization after MOCA was higher, ranging across time points in the various studies from .9.77 (1 month) to 2.20 (24 months). The odds of recanalization at 12 months was 3.65 times higher after MOCA than among people who had RFA (95% CI 1.34–9.93, Figure 4a). This corresponds to a 15% (absolute) increase in recanalization with MOCA than with RFA at 12-month follow-up (95% CI 7%–22%; Figure 4b).

A similar picture emerged for MOCA versus EVLA: the pooled odds of recanalization were 5.75 higher with MOCA compared with EVLA (95% CI 1.97–16.79; Figure 5a). The corresponding increase in (absolute) recanalization with MOCA was 18% at 12 months compared with EVLA (95% CI 10%–26%; Figure 5b).

We rated the quality of the evidence for recanalization after MOCA compared with RFA (Table A6) and EVLA (Table A5) as moderate, rating down for risk of bias.

Table 5: Procedure Failure, Recanalization, and Retreatment: Mechanochemical Ablation vs. Thermal Ablation

Author, Year (Study Design)	Procedure Failure, %	Reason(s)	Partial or Complete Recanalization, % (n/N)	Reintervention
Mohamed et al, 2020[83] (RCT)	*MOCA* 0 *EVLA* 3 (n = 2/69)	— User error[a] (n = 1) Warfarin + large GSV diameter (n = 1)	*At 12 mo:* *MOCA* 1 (1/69) complete; 12 (8/69; segment recanalization with reflux); 10 (7/69; recanalization no reflux) *EVLA* 4 (3/69; complete proximal thigh); 1 (1/69, distal knee with reflux)	2 patients with total recanalization were retreated with EVLA (successful) All others asymptomatic at 1-y follow-up, no reintervention
Vahaaho et al, 2019, 2020[80,85] (RCT)	NR	NR	*At 12 mo:* *MOCA* 18 (10/55; 1 complete GSV, 1 partial; 5 proximal; 3 in thigh only) *RFA* 0/29 *EVLA* 0/33	*Within 36 mo:* *MOCA* 1 EVLA, 1 sclerotherapy (branch varicosities), 2 awaiting EVLA, "a few" awaiting consultation for possible additional GSV treatment *EVLA* none *RFA* 2 scheduled for treatment of branch varicosities
Holewijn et al, 2019[79] (RCT)	*MOCA* 0.9 (n = 1; immediate)	Could not cannulate GSV	*At 30 d:* *MOCA* 4/103 (complete); 5/103 (partial) *RFA* 1/103 (partial) (*P* = .100) *At 1 y:* *MOCA* 15/81 (16.5%) *RFA* 5/72 (5.8%) (*P* = .025) *At 2 y* *MOCA 21/76 (20%)* *RFA* 12/81 (11.7%) (*P* = .066)	3 MOCA recurrence patients cross over to get RFA *Reintervention in 1–3 y:* *MOCA* 1.3% *RFA* 1.3% *Reintervention until 2 y:* *MOCA 2.9%* *RFA* 2.0% *Future reintervention scheduled:* *MOCA* 1.4% *RFA* 5.1%
Vun et al, 2015[76] (NRS)	NR	NR	*At 4–6 wk:* *MOCA* 3/55 complete; 2/55 partial *RFA* NR[b] *EVLA* NR[b]	NR

Notes for Table 5:

Abbreviations: d, day(s); EVLA, endovenous laser ablation; mo, month; GSV, great saphenous vein; mo, month(s); MOCA, mechanochemical ablation; n, number of people; N, total number of people in group; NR, not reported; NRS, nonrandomized study; RCT, randomized controlled trial; RFA, radiofrequency ablation; wk, week(s); y, year(s).

[a]Reported that EVLA machine was not set up correctly.[83]

[b]Referenced another study for proportion of technical success for RFA and EVLA.[76]

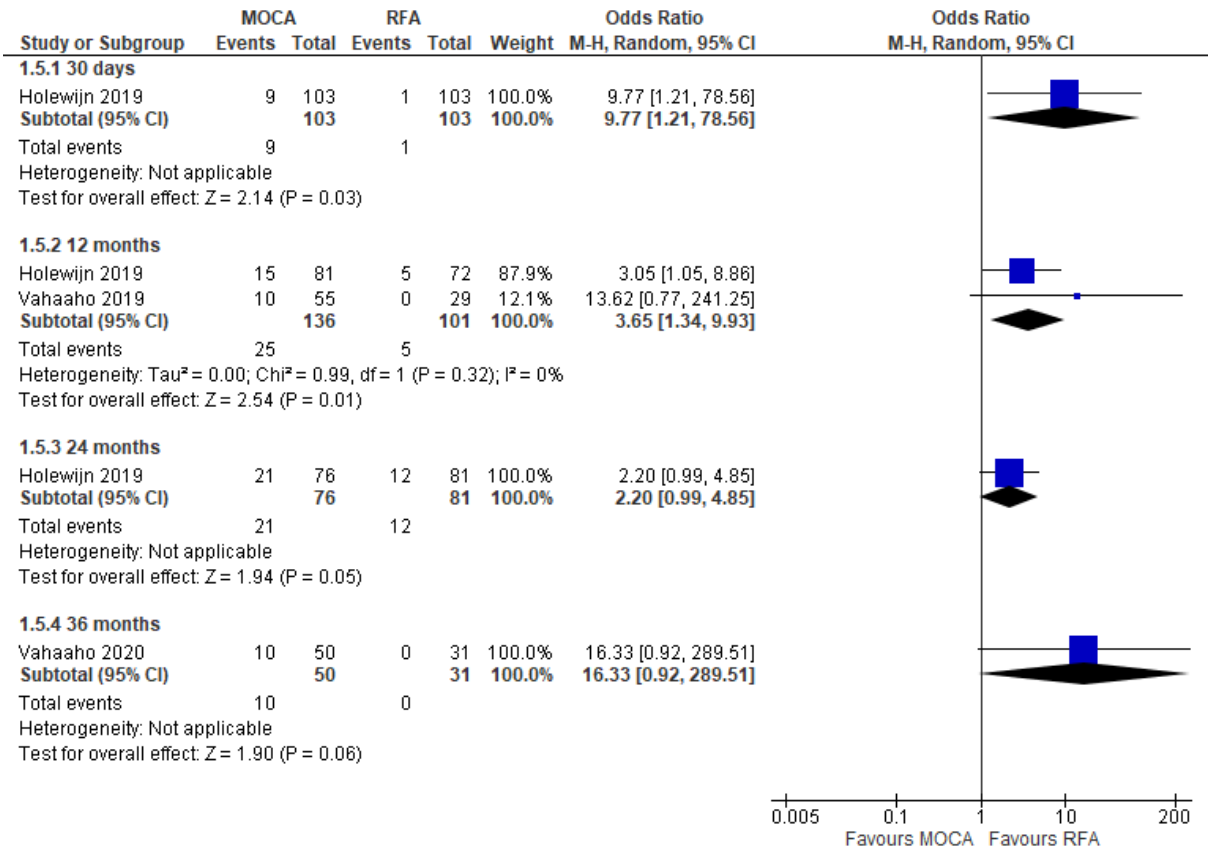

Figure 4a: Odds of Complete or Partial Recanalization of Treated Vein After Mechanochemical Ablation or Radiofrequency Ablation

Abbreviations: CI, confidence interval; Mantel-Haenszel; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.
Event is total vein closure. A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the populations in the studies by Holewijn et al[79] and Vahaaho et al, 2019.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.
Data sources: Holewijn et al, 2019[79]; Vahaaho et al, 2019[80] and 2020.[85]

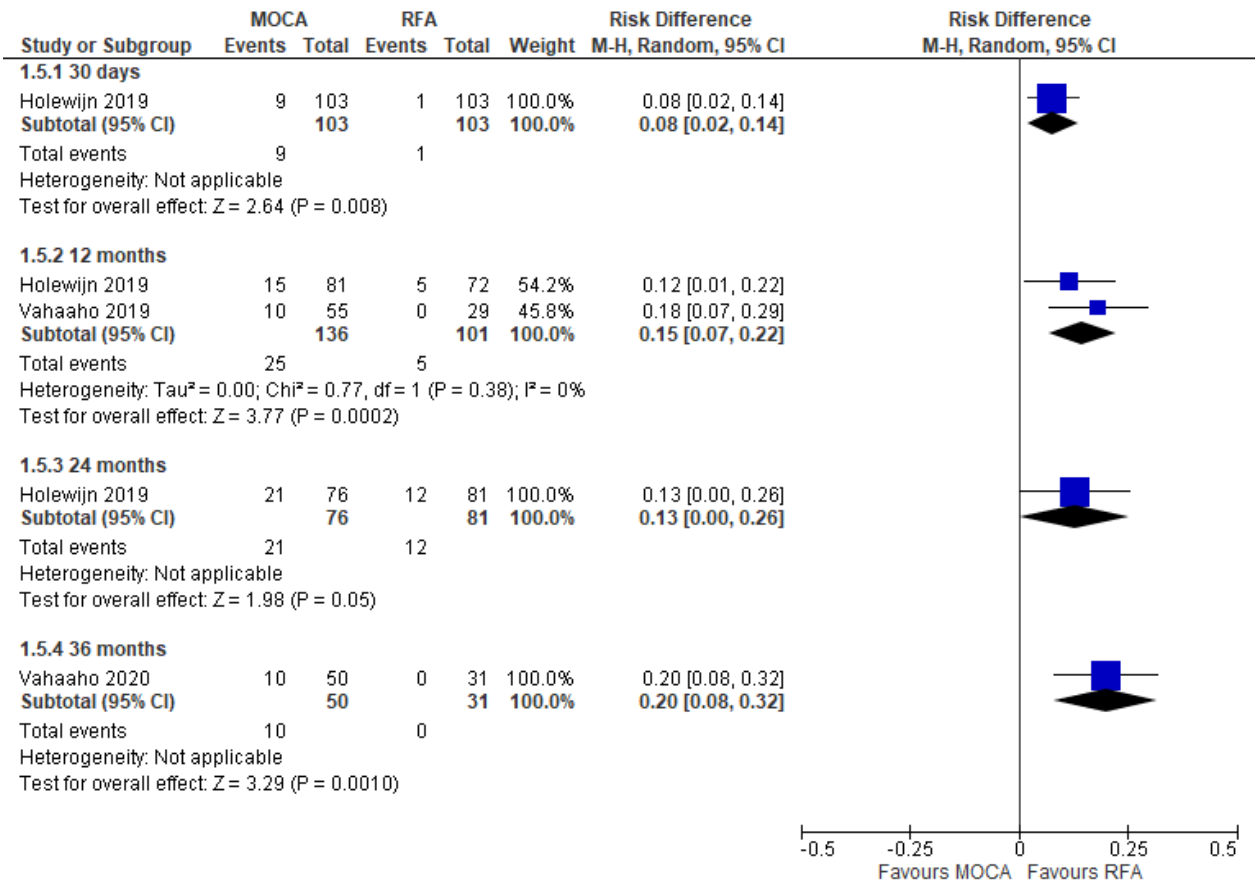

Figure 4b: Risk Difference for Complete or Partial Recanalization of Treated Vein After Mechanochemical Ablation or Radiofrequency Ablation

Abbreviations: CI, confidence interval; Mantel-Haenszel; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.
Event is total vein closure. A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the populations in the studies by Holewijn et al[79] and Vahaaho et al, 2019.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.
Data sources: Holewijn et al, 2019[79]; Vahaaho et al, 2019[80] and 2020.[85]

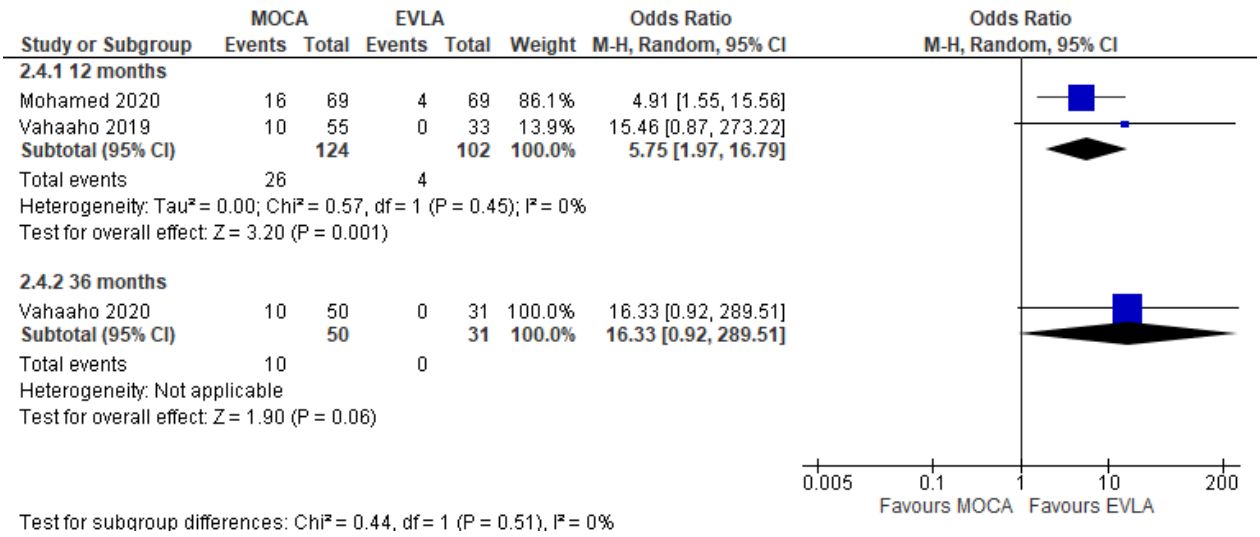

Figure 5a: Odds of Complete or Partial Recanalization of Treated Vein After Mechanochemical Ablation or Endovenous Laser Ablation

Abbreviations: CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel; MOCA, mechanochemical ablation.

Events occurred over 12-month study duration. A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the trials by Mohamed et al[83] and Vahaaho et al, 2019.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Mohamed et al, 2020[83]; Vahaaho et al, 2019[80] and 2020.[85]

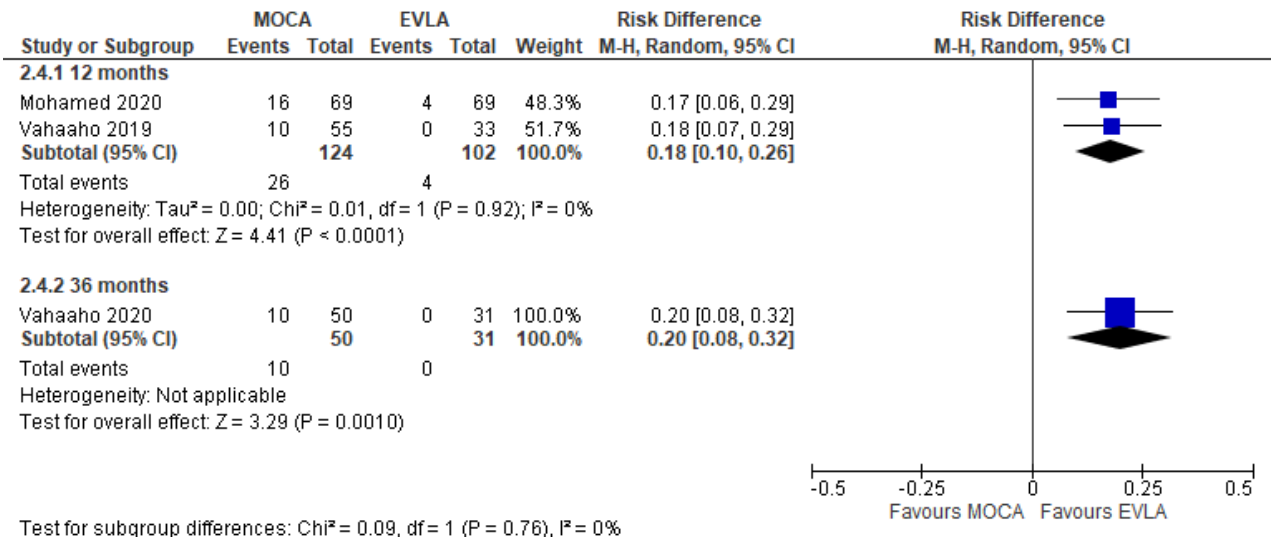

Figure 5b: Risk Difference for Complete or Partial Recanalization of Treated Vein After Mechanochemical Ablation or Endovenous Laser Ablation

Abbreviations: CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel; MOCA, mechanochemical ablation.

Events occurred over 12-month study duration. A random effects model was used for our meta-analysis because the distribution of venous disease severity differed between the trials by Mohamed et al[83] and Vahaaho et al, 2019.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Mohamed et al, 2020[83]; Vahaaho et al, 2019[80] and 2020.[85]

Change in Clinical Symptoms

Clinical symptoms in all studies were measured by the Venous Clinical Severity Score (VCSS).[86,87] The VCSS rates 10 clinical descriptors (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, number of active ulcers, duration of active ulceration, size of ulcer, and compressive therapy use) from 0 to 3. The maximum total score is 30 points, with higher scores reflecting greater severity of venous disease. The tool has been validated and can be used to predict treatment response and assess changes after treatment.

MOCA VERSUS EVLA

One RCT[83] reported the change in VCSS for people who received either MOCA or EVLA. At 1-year follow-up, both groups had statistically significant improvement from baseline ($P < .001$).[83] There was no significant difference in the improvement between groups at any time point (Table 6).

Table 6: Venous Clinical Severity Score After Mechanochemical Ablation vs. Endovenous Laser Ablation

Author, Year	Baseline VCSS, Median (IQR)		Follow-Up Time Point	Follow-Up VCSS, Median (IQR)		*P* Value
	MOCA	EVLA		MOCA	EVLA	
Mohamed et al, 2020[83] (RCT)	6 (5–8)[a]	6 (5–7)[a]	1 wk	0 (0–1)[a]	1 (0–2)[a]	NS[b]
			6 wk	0 (1–2)[a]	2 (0–2)[a]	NS[b]
			6 mo	0 (0–1)[a]	0 (0–1)[a]	NS[b]
			1 y	0 (0–1)[a]	0 (0–1)[a]	NS[b]

Abbreviations: EVLA, endovenous laser ablation; mo, month(s); MOCA, mechanochemical ablation; NR, not reported; NS, not statistically significant; VCSS, Venous Clinical Severity Score; wk, week(s); y, year.

[a]Estimated from visual inspection of Figure 6 in Mohamed et al.[83]

[b]Reported as no statistically significant difference at $P < .01$.

MOCA VERSUS RFA

Three studies (two RCTs[74,79] and one nonrandomized prospective cohort[75]) reported on the improvement in VCSS after either MOCA or RFA. All the studies noted statistically significant improvement of clinical symptoms within each group at every follow-up time. Baseline VCSS scores were comparable in all studies. In the study by Holewijn et al,[79] the VCSS component of ankle edema was higher at baseline in the RFA group (10.7% vs. 0% in MOCA, $P = .002$). The baseline and post-treatment results are in Table 7.

Table 7: Venous Clinical Severity Score After Mechanochemical Ablation vs. Radiofrequency Ablation

Author, Year (Study Design)	Baseline Score, Median (IQR)		Follow-Up Time Point	Follow-Up Score, Median (IQR)		*P* Value
	MOCA	RFA		MOCA	RFA	
Holewijn et al, 2019[79] (RCT)	4.9 (0.50–10.3)[a]	5.3 (0.46–11.1)[a]	4 wk	1.8 (0.32–3.8)[a]	2.6 (0.37–5.49)[a]	.001
			1 y	1.8 (0.39–3.90)[a]	1.7 (0.36–3.69)[a]	.696
			2 y	1.0 (1 –2.99)	1.0 (1–3)	.882
Lane et al, 2017; Bootun et al, 2016[73,74] (RCT)	6 (NR)	5 (NR)	1 mo	2 (range 1–4)	3 (range 1–5)	.096
			6 mo	2 (range 1–4)	2 (range 1–5)	.536
van Eekeren et al, 2013[75] (prospective comparative cohort)	3.0 (2.75–5.25)	4.0 (3–7)	4–6 wk	1 (1–2)	3 (1.25–3.75)	.21

Abbreviations: IQR, interquartile range; mo, month(s); MOCA, mechanochemical ablation; NR, not reported; RCT, randominzed controlled trial; RFA, radiofrequency ablation; wk, week(s); y, year.

[a]Estimated from Figure 3 in Holewijn et al[79] using WebPlotDigitizer software.[43]

In the RCT by Holewijn et al,[79] at 1-month follow-up improvement was greater in the MOCA group than the RFA group. However, at the subsequent time points of 1 and 2 years, there was no difference in clinical symptom improvement between groups. The other RCT[75] and the nonrandomised study[75] both found no differences between MOCA and RFA groups in clinical symptom improvement at any time point (Table 7).

Van Eekeren et al[75] also reported the proportion of treated legs with improved, unchanged, or deteriorated outcomes at 6 weeks post-treatment, categorized based on VCSS. In the MOCA group, 82% of treated legs showed improvement, 15% had no change in VCSS score, and 3% exhibited deterioration.[75] Similarly in the RFA group, 72% showed improvement, 16% were unchanged, and 12% deteriorated after treatment.

In addition to VCSS, Lane et al[74] measured the effect of venous disease on work-based disability using Venous Disability Score. The groups had comparable scores at baseline and the authors describe no differences in Venous Disability Score between groups at 1- or 6-month follow-up (data and *P* value not reported).

We rated the quality of the evidence for change in clinical symptoms after MOCA compared with RFA as high (Appendix 2, Table A6), and moderate compared with EVLA, downgrading for risk of bias and imprecision (Table A5).

MOCA VERSUS EVLA AND RFA

In their 2020 update of RCT results, Vahaaho et al[85] only reported VCSS data for patients who completed 3 years of follow-up. Based on the figures in the publication, mean VCSS scores decreased within groups from baseline in the MOCA, RFA, and EVLA groups (6.4, 6.2, and 6.3 respectively) compared with 3 years (mean 2.1, 1.7, and 2.1 respectively, *P* value not reported). No differences were seen at any time in VCSS between the groups.[85]

Quality of Life

Both disease-specific and generic health-related quality of life measures are used for research on chronic venous disease. The Aberdeen Varicose Vein Questionnaire (AVVQ) is the most used patient-reported outcome measure for disease-specific quality of life in this field. It is composed of 13 questions specific to varicose veins related to experience of symptoms, symptom management, visible skin changes, and impact on a person's daily choices and activities.[88] The maximum score is 100, with higher scores indicating worse quality of life.[89] Some previous studies considered that 5 points on the AVVQ may reflect a clinically meaningful threshold of change in quality of life.[74]

In addition to the AVVQ, some studies also use one or more formats of generic quality-of-life tools, such as the 36-Item Short Form Health Survey (SF-36)[90] or EuroQol 5 Dimensions (EQ-5D) questionnaire.[91]

MOCA VERSUS EVLA

One RCT assessed both disease-specific quality of life and generic quality of life in people who had treatment with either MOCA or EVLA.[83] The AVVQ scores within groups improved from baseline at 1 year ($P < .001$). The between-groups analysis employed a repeated measures ANOVA with a Bonferroni correction for multiple comparisons. There were no differences in improvement in either disease-specific or generic quality of life at any time point (Table 8).

Table 8: Quality of Life Score After Mechanochemical Ablation vs. Endovenous Laser Ablation

Author, Year (Study Design)	Baseline Score, Median (IQR)		Follow-Up Time Point	Follow-Up Score, Median (IQR)		*P* Value
	MOCA	EVLA		MOCA	EVLA	
Disease-Specific Quality of Life: AVVQ						
Mohamed et al, 2020[83] (RCT)	13.1[a] (9.8–16.4)[a]	15.3[a] (10.1–20.1)[a]	1 wk	13.1[a] (8.3–18.3)[a]	13.5[a] (8.2–17.2)[a]	.677
			6 wk	3.6[a] (1.4–7.2)[a]	4.1[a] (1.5–7.6)[a]	.602
			6 mo	2[a] (0–4.9)[a]	2[a] (0–5)[a]	.911
			1 y	2.0[a] (0.0–4.8)[a]	2.0[a] (0.0–5.3)[a]	.437
Generic Quality of Life: EQ-5D						
Mohamed et al, 2020[83] (RCT)	0.851 (.806–.877)	0.837 (0.772–.877)	1 wk	.880[b] (.827–.997)[b]	.860[b] (.790–.997)[b]	.340
			6 wk	1[b] (.879–1)[b]	1[b] (.880–1)[b]	.734
			6 mo	1[b] (.983–1)[b]	1[b] (.888–1)[b]	.076
			1 y	1[b] (.878–1)[b]	1[b] (.879–1)[b]	.991

Abbreviations: AVVQ, Aberdeen Varicose Vein Questionnaire; EQ-5D, EuroQol 5-Dimensions questionnaire; EVLA, endovenous laser ablation; IQR, interquartile range; mo, month(s); MOCA, mechanochemical ablation; RCT, randomized controlled trial; wk, week(s); y, year.

[a]Estimated from Figure 4 in Mohamed et al[83] using WebPlotDigitizer software.[43]

[b]Estimated from Figure 5 in Mohamed et al[83] using WebPlotDigitizer software.[43]

MOCA VERSUS RFA

Three studies assessed people's quality of life before and after treatment.[74,75,79] All studies measured disease-specific quality of life, as well as generic health-related quality of life. Baseline disease-specific quality of life was similar across intervention groups in all studies ($P > .05$), and there were no differences between groups in post-treatment quality of life (Table 9).

Table 9: Quality of Life Score After Mechanochemical Ablation vs. Radiofrequency Ablation

Author, Year (Study Design)	Baseline Score, Median (IQR)		Follow-Up Time Point	Follow-Up Score, Median (IQR)		*P* Value
	MOCA	RFA		MOCA	RFA	
Disease-Specific Quality of Life: AVVQ						
Holewijn et al, 2019[79] (RCT)	14.3 (2.75–31.25)[a]	13.31 (3.16–29.72)[a]	4 wk	8.9 (2.12–19.85)[a]	7.6 (2.19–17.20)[a]	.223
			1 y	7.5 (2.05–16.93)[a]	7.0 (2.4–16.44)[a]	.753
			2 y	5 (3.23–17.90)[a]	4.8 (3.44–16.02)[a]	.573
Lane et al, 2017; Bootun et al, 2016[73,74](RCT)	18.89[b] (NR)	19.55[b] (NR)	1 mo	12.1[b] (7.3–21.2)[b]	12.9[b] (6.6–20.4)[b]	.799
			6 mo	11.8[b] (7.2–20.5)[b]	9.4[b] (3.6–21.4)[b]	.511
Van Eekeren et al, 2013[75] (prospective comparative cohort)	7.1 (5.3–9.2)	9.5 (4.5–16.4)	6 wk	5.0 (3–8.5)	4.5 (1.5–11.2)	.17
Generic Quality of Life: EQ-5D						
Lane et al, 2017; Bootun et al, 2016[73,74] (RCT)	.761 (NR)[c]	.730 (NR)[c]	1 mo	.761 (0.659–1)	.761 (.690–1)	.939
			6 mo	.761 (.690–1)	.761 (.486–1)	.125
Generic Quality of Life: EQ-5D VAS						
Lane et al, 2017; Bootun et al, 2016[73,74] (RCT)	80.0 (NR)	84.5 (NR)	1 mo	85 (60–95)[d]	87 (80–90)[d]	.227
			6 mo	85 (60–93)[d]	89 (70–95)[d]	.302

Abbreviations: AVVQ, Aberdeen Varicose Vein Questionnaire; EQ-5D, EuroQol 5-Dimensions questionnaire; EVLA, endovenous laser ablation; IQR, interquartile range; mo, month(s); MOCA, mechanochemical ablation; NR, not reported; NS, not significant; RCT, randomized controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale; wk, week(s); y, year.

[a]Estimated from Figure 4 in Holewijn et al[79] using WebPlotDigitizer software.[43]

[b]Scores presumed to be medians and interquartile ranges as per Table 1 and boxplot in Figure 4 of Lane et al.[74] Baseline and 1-month follow-up also reported as mean score and standard deviation in Table 3 of earlier publication by Bootun et al[73] with no differences between groups at baseline or follow-up ($P > .05$).

[c]Between-group difference at baseline was not significant ($P = .989$).

[d]Scores in parentheses presumed to reflect IQR based on article stating that data are reported as medians.[74]

As shown in Table 9, Lane et al[74] administered two forms of the EQ-5D: a questionnaire (3-level version) and a visual analogue scale (VAS). The baseline quality of life of participants appeared poorer than in other studies; the authors suggest this may be owing to more severe venous disease in this study cohort (median CEAP was 4; see Table 3). No differences on the questionnaire emerged between intervention groups at baseline or any follow-up time. With the EQ-5D VAS, at baseline there was a trend toward higher scores in the RFA group ($P = .050$), but no difference between groups at 1 or 6 months.[74]

Holewijn et al[79] also had patients complete the SF-36 health survey. The authors report no difference between groups at baseline. Four weeks after the procedures, the MOCA and RFA groups had similar SF-36 scores except that the energy/fatigue score was slightly higher (better) in the RFA group. At

subsequent 1- and 2-year follow-up, the groups scored similarly on all domains of the SF-36 (*P* not reported). Similarly, van Eekeren et al[75] administered a version of the SF-36 to assess quality of life, finding no differences on any of the domains between MOCA and RFA groups before intervention or at 6-week follow up.

MOCA VERSUS EVLA AND RFA

One RCT compared disease-specific quality of life 1 year after three endovenous procedures: MOCA, RFA, and EVLA.[80] Baseline AVVQ scores were comparable (Table 10; *P* = .952). Each group's quality of life improved significantly from baseline at both 1- and 3-year follow-up; however, there was no difference in the quality-of-life improvements between the three interventions at any time.

Table 10: Quality of Life Score After Mechanochemical Ablation vs. Thermal Endovenous Ablation

Author, Year (Study Design)	Procedure	Baseline, Mean AVVQ	1-Y Follow-Up, Mean AVVQ	*P* Value	3-Y Follow Up, Mean AVVQ	*P* Value
Vahaaho et al, 2019[80] and 2020[85] (RCT)	MOCA	15.8	6.2	.901	8.1[a]	.467
	RFA	17.2	6.8		6.8[a]	
	EVLA	16.1	5.3		6.0[a]	

Abbreviations: AVVQ, Aberdeen Varicose Vein Questionnaire score; EVLA, endovenous laser therapy; MOCA, mechanochemical ablation; RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]Values estimated from Figure 6 in Vahaaho et al, 2020[85] using WebPlotDigitizer software.[43]

We rated the quality of the evidence for quality of life after MOCA compared with RFA as low, rating down for risk of bias (Appendix 2, Table A6), and high compared with EVLA (Table A5).

Patient Satisfaction

Two studies reported patient satisfaction. Both were RCTs, one compared MOCA with EVLA[83] while the other compared it with RFA.[79] A 100-mm visual analogue scale was used to assess overall and cosmetic satisfaction in the trial by Mohamed et al.[83] The study comparing MOCA with RFA did not provide details on the measure of patient satisfaction used in the study.[79]

Both studies found no statistically significant difference between MOCA or comparator groups in patient satisfaction after treatment (Table 11).

Table 11: Patient Satisfaction After Mechanochemical Ablation vs.Thermal Endovenous Ablation

Author, Year (Study Design)	Comparator	Satisfaction Measure (Time Point)	Score, MD (Range)		*P* Value
			MOCA	Comparator	
Mohamed et al, 2020[83] (RCT)	EVLA	100-mm VAS[a] (1 y)			
		Overall	97 (91–100)	100 (90–100)	.385
		Cosmetic	91 (87–100)	98 (90–100)	.084
Holewijn et al, 2019[79] (RCT)	RFA	NR (30 d)	9.0 (8–9)	8.0 (8–9)	.077

Abbreviations: d, day(s); EVLA, endovenous laser ablation; MD, median; MOCA, mechanochemical ablation; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale; y, year.

[a]Maximum score is 100 and reflects overall satisfaction with the result or cosmetic result.[83]

We rated the quality of the evidence for patient satisfaction after MOCA compared with RFA as high (Appendix 2, Table A6), and moderate compared with EVLA, downgrading for risk of bias (Table A5).

Recovery Time

The length of time patients were unable to work or participate in their normal activities after MOCA compared with EVLA or RFA was assessed by four RCTs[74,79,80,83] and one comparative cohort study[75] (Table 12). Time to return to work, where reported, reflected only a subset of the study participants (i.e., those who were employed). Recovery times were similar between groups, except in the nonrandomized study which reported statistically significantly fewer days off work and activities in the MOCA group compared with RFA.[75]

Table 12: Recovery Time After Mechanochemical Ablation vs. Thermal Ablation

Author, Year (Study Design)	Procedure	Days Off Work, MD[a] (IQR)	*P* Value	Time to Normal Activity, Days	*P* Value
Mohamed et al, 2020[83] (RCT)	MOCA	6 (3–10)	.725	2 (1–4)	.127
	EVLA	5 (2–10)		3 (1–7)	
Vahaaho et al, 2019[80] (RCT)		*Initial prescribed sick leave, MN*			
	MOCA	4.3	.841	NR	NR
	EVLA	5.3			
	RFA	4.7			
		No. of additional days needed			
	MOCA	NR	.402	NR	NR
	EVLA	NR			
	RFA	NR			
Holewijn et al, 2019[79] (RCT)	MOCA	1 (1–3)[b]	.129	1 (0–1)[c]	.085
	RFA	2 (1–4)[b]		1 (1–2)[c]	
Lane et al, 2017; Bootun et al, 2016[73,74] (RCT)	MOCA	3 (1–7)	NS	2 (1–4)	NS
	RFA	2 (2–7)		2 (1–7)	
van Eekeren et al, 2013[75] (prospective comparative cohort)	MOCA	1 (1–3.75)	.02	1 (0–1)	.01
	RFA	2 (2–7)		1 (1–3)	

Abbreviations: EVLA, endovenous laser ablation; IQR, interquartile range; MD, median; MN, mean; MOCA, mechanochemical ablation; No., number; NR, not reported; NS, not significant; RFA, radiofrequency ablation.

[a]Unless otherwise stated.

[b]Range for return to work reported to be 0 to 13 days for MOCA and 0 to 15 days for RFA.[79]

[c]Range for restart of daily activities reported to be the same for both MOCA and RFA (0 to 6 days).[79]

We rated the quality of the evidence for recovery time after MOCA compared with RFA as low, rating down for risk of bias and imprecision (Appendix 2, Table A6), and moderate compared with EVLA, downgrading for imprecision (Table A5).

Complications

The reporting of major and minor complications varied substantially across studies and the data presented here reflect those available from each study. Data were largely descriptive and between-groups occurrences were rarely tested statistically. Major complications reflect the more serious adverse events observed during the study periods (Table 13). Minor complications are less serious and tend to be more common (Table 14).

MAJOR COMPLICATIONS

One of the potentially serious complications following all endovenous procedures and surgery is deep vein thrombosis (DVT), a blood clot blocking blood flow in the deep veins. Moon et al[77] specifically designed a study to examine adverse effects of microbubble in the heart and neurological symptoms

during or 30 minutes after a MOCA or RFA procedure (see Table 13). A microbubble is a contained, small amount of gas which has the potential to travel through the circulatory system and result in embolism or stroke. A microbubble can be detected (visually) with echocardiogram. Neurological symptoms were also examined by questionnaire immediately or 30 minutes after the procedure. No symptoms were identified in any of the patients in the study.[77] Kim et al[78] reported two readmissions to hospital for infections unrelated to the access site, one nonocclusive (partially blocked) DVT, and one late death unrelated to the procedure (pneumonia in the context of advanced colon cancer), but it is unclear in which treatment group these occurred.

Table 13: Major Complications After Mechanochemical Ablation vs. Thermal Ablation

Author, Year (Study Design)	Complication	Frequency or %		*P* Value
		Comparator(s)	MOCA	
Mohamed et al, 2020[83] (RCT)	DVT	*EVLA* 0	2 (1 person)[a]	NR
Kim et al, 2019[78] (retrospective chart analysis)		*Thermal ablation*[b,c]		.6612
	Post-procedural DVT	3.45%	1.89%	
Vahaaho et al, 2019, 2020 [80,85] (RCT)	DVT at 1 mo	*EVLA* 0	0	NR
		RFA 0		
Holewijn et al, 2019[79] (RCT)		*RFA*	0	NR
	Procedure-related SAEs at 30 d	0		
	Cardiac SAEs through 2 y	1[d]	1[e]	
	DVT	1[f]	0	
Moon et al, 2017[77] (Prospective cohort)	Microbubble in right heart[g]	*RFA* 5/17 (29%)	4/11 (36%)	.8065
Lane et al, 2017[74] (RCT)	DVT	*RFA* 1 (1.2%)	1 (1.2%)	NS
van Eekeren et al, 2013[75] (prospective comparative cohort)	Major complications	*RFA* 0	0	NR

Abbreviations: d, day(s); DVT, deep vein thrombosis; EVLA, endovenous laser therapy; mo, month; MOCA, mechanochemical ablation; NR, not reported; NS, not significant; RFA, radiofrequency ablation; SAE, serious adverse event; SSV, small saphenous vein; y, year(s).

[a]Ipsilateral occlusive DVT in a gastrocnemius vein and a nonocclusive femoral vein DVT detected at 1 week after SSV MOCA (asymptomatic) that were treated with 2 weeks' dose of low-molecular weight heparin. Duplex ultrasound repeated 3 weeks post-procedure showed complete resolution.[83]

[b]RFA and EVLA groups combined for comparison.[78]

[c]Complications included hospital readmission of 2 people with infections (not access related), 1 nonocclusive DVT, and 1 late death secondary to pneumonia in colon cancer (unrelated to procedure).[78]

[d]Patient was hospitalized for unstable angina and had coronary bypass surgery.[79]

[e]Patient was hospitalized for ventricular fibrillation and treated with cardioversion.[79]

[f]DVT seen on duplex ultrasound at 1 year but there were no clinical consequences.[79]

[g]All microbubbles were classified as Grade 1 except for 1 person in the RFA group.[77]

As summarized in Table 13, the number and nature of serious adverse events observed across the studies were generally similar after MOCA, EVLA, or RFA. In limited cases where statistical comparisons between groups were performed, there were no differences.

MINOR COMPLICATIONS

The most common minor complications reported after thermal and nonthermal endovenous procedures were skin pigmentation changes, palpable localized lumps (skin induration, a thickening and hardening of the skin), and superficial phlebitis (inflammation in a vein). Overall, the occurrence of minor complications was similar across thermal endovenous procedures and MOCA. One study documented that hyperpigmentation was more common in the MOCA group than in the RFA group (7 occurrences vs. 2, *P* = .038).[79] Sensory disturbances (nerve injury or saphenous neuralgia) tended to occur slightly more often after thermal ablation in some studies.[79,80,83]

Van Eekeren et al[75] noted that three patients reported pain after 2 weeks. The authors report that one of these people had thrombophlebitis, and another had induration, without mention of the third person.[75] Their median deterioration in VCSS was 1.0 (IQR 1–2).

Table 14: Minor Complications After Mechanochemical Ablation vs. Thermal Ablation

Author, Year (Study Design)	Complication	Frequency or %		*P* Value
		Comparator(s)	MOCA	
Mohamed et al, 2020[83] (RCT)	Phlebitis	*EVLA* 5/69 (7%)	9/69 (13%)	.262
	SSI at phlebectomy site	1/69 (1%)	1/69 (1%)	.992
	Skin staining (throughout follow-up)	4/69 (6%)	9/69 (13%)	.139
	Sensory disturbance	6/69[a] (8.7%)	2/69[a] (2.9%)	.151
Kim et al, 2019[78] (retrospective chart analysis)	Post-procedural complications	*Thermal ablation*[b] 12%	4.89%	.0598
Vahaaho et al, 2019[80] (RCT)	*At 1 mo*	Sensory disturbance *EVLA* 4/33; *RFA* 1/29	Superficial infection[c] 1/55	NS[d]
	At 1 y Sensory disturbance (area < 10 cm^2)	*EVLA* 3/33; *RFA* 2/29	0/55	.090[e]
	New pigmentation[f]	*EVLA* 3/33; *RFA 4/29*	6/55	987
	Local lump (< 5 cm^2)	*EVLA* 0/33; *RFA* 3/29	1/55	.055
	At 3 y Sensory disturbance (area < 10cm^2), persisting from 1 y	*EVLA* 2; *RFA* 1	0	NR

Author, Year (Study Design)	Complication	Frequency or %		*P* Value
		Comparator(s)	MOCA	
Holewijn et al, 2019[79] (RCT)	*Up to 30 d*	*RFA*		
	Total no. complications	63	62	.257
	No. patients with ≥ 1 complication	42 (40.8%)	35 (34%)	.339
	Superficial thrombophlebitis	8	12	.129
	Induration	12	17	.071
	SSI	2	0	.191
	Saphenous neuralgia	3	1	.399
	Pain > 1 wk	17	10	.276
	Hematoma	15	14	.699
	Skin burn	0	0	NA
	Hyperpigmentation	2	7	.038
	Swelling and fever	1	0	NR
	Ulcer re-opened	1	0	NR
	Blister at plaster site	1	0	NR
Lane et al, 2017[74] [74] (RCT)		*RFA*		
	Minor phlebitis	2	3	NS
	Sensory disturbance	0	0	
van Eekeren et al, 2013[75] (prospective comparative cohort)		*RFA*		
	Hematoma	4 (12%)	2 (6%)	.67
	Paresthesia	0	0	NA
	Thrombophlebitis	2 (6%)	0	.49
	Induration	8 (24%)	4 (12%)	.20
	Hyperpigmentation	3 (9%)	3 (9%)	1.0

Abbreviations: d, day; EVLA, endovenous laser therapy; mo, month(s); MOCA, mechanochemical ablation; NA, not applicable; no, number; NR, not reported; NS, not significant; RCT, randomized controlled trial; RFA, radiofrequency ablation; SSI, surgical site infection; wk, week(s); y, year(s).

[a]Sensory disturbance due to concomitant phlebectomy. At 1 year, 1 patient resolved, 1 lost to follow-up, and 6 still had symptoms that did not interfere with activities of daily living.[83]

[b]RFA and EVLA combined for comparisons.[78]

[c]Treated with oral antibiotics.[80]

[d]No significant differences between MOCA, EVLA, or RFA in the frequency of hematoma, pigmentation, or palpable lumps at 1 month.[80]

[e]*P* value is for all subtypes of nerve injury combined, across treatment groups: sensory disturbance, shin, thigh and none.[80]

[f]Pigmentation includes distribution of no changes, old changes, new in the lower calf, and new in the upper calf.[80]

Cyanoacrylate Adhesive Closure

Characteristics of Included Studies

We included a total of 11 studies (two RCTs[65,81] and nine nonrandomized studies[48,62-64,66-68,82,92] reported in 14 publications) on CAC (Table 15). Eight studies compared CAC with either RFA or EVLA or both,[48,63-68,81] and two multi-arm studies compared CAC with RFA, two types of EVLA (with different laser wavelengths: 980 nanometers [nm] or 1470 nm), and surgical vein stripping.[62,82] Seven of the studies were from Turkey,[48,62,64-66,68,82] and used either the VariClose[48,62,64,65,68,82] or VenaBLOCK[66] CAC devices. The other studies came from the United States (n = 1[81]) and Canada (n = 2[63,67]) and used the VenaSeal CAC device.

The target vein for treatment was the GSV in all but one study, which examined CAC treatment for SSV insufficiency alone.[82] Two studies also treated the anterior accessory saphenous vein or perforator veins,[62,63] or SSV[65] in addition to GSV, as indicated for patients. Mean GSV diameters ranged across studies from just under 6 mm to over 9 mm, except for Kubat et al, 2019[62] which only included patients with veins of ≥ 10 mm diameter. Venous disease severity was predominantly C2 to C3 in most study populations (Table 15). The ages of participants were typically between 40 and 60 years, and were comparable across intervention groups in all studies. A sole study reported on the ethnic composition of the study participants, with approximately 12% to 15% reported to be Hispanic or nonwhite.[48]

Risk of Bias in the Included Studies

The VeClose RCT[69-72,81] was judged to be at low risk of bias in all domains of the Cochrane Risk of Bias tool. There were some concerns with deviations from the intended interventions in the RCT by Eroglu and Yasim[65] (Appendix 2, Table A2).

All nine nonrandomized studies were judged to be at either unclear or high risk of bias on one or more of the dimensions (Appendix 2, Table A4). Four studies were at unclear risk of bias for blinding of outcome assessments.[62,64,66,68] The study by Yang et al[63] was judged to be at unclear risk of bias for consideration of confounding variables and at high risk of bias for incomplete outcome data. The study by Koramaz et al[68] was judged to be at high risk for selection of participants and unclear risk of bias for blinding of outcome assessments. Both blinding of outcome assessment and incomplete outcome data were judged to be at unclear risk of bias for the study by Ovali and Sevin.[66] Two studies were rated as unclear risk of bias only for incomplete outcome data (Bozkurt and Yilmaz[48]; McGuinness et al[67]). Two studies were judged to be at unclear risk of bias only due to lack of blinding of outcome assessments.[62,64] One study was judged to be at high risk of bias due to potentially confounding variables, and risk of bias was unclear on blinding of outcome assessment and selective reporting of outcomes.[92]

Table 15: Characteristics of Included Studies—Cyanoacrylate Adhesive Closure

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, %		Age, Mean (SD), Y	
			CAC	Comparator(s)	CAC	Comparator(s)	CAC	Comparator(s)
Compared With RFA, EVLA, and Surgical Vein Stripping (HLS)								
Kubat et al, 2020[82]	Retrospective chart analysis (Turkey)	SSV only *CAC* 5.83 (± 1.44) *HLS* 7.07 (± 1.99) *EVLA 980 nm* 6.5 (± 1.68) *EVLA 1470 nm* 6.98 (± 1.97) *RFA* 6.65 (± 2.13)	28	*HLS* 44 *EVLA 980 nm* 39 *EVLA 1470 nm* 36 *RFA* 28	C2: 53.6 C3: 28.6 ≥ C4: 17.9 < C2 and > C5 excluded	*HLS* *C2: 52.3* C3: 29.5 C4: 18.2 *EVLA 980 nm* C2: 66.7 C3: 28.2 C4: 5.1 *EVLA 1470 nm* C2: 66.7 C3: 13.9 C4: 19.4 *RFA* C2: 47.1 C3: 30.6 C4: 22.3	42.96 (± 14.04)	*HLS* 44.98 (± 10.88) *EVLA 980 nm* 44.54 (± 13.62) *EVLA 1470 nm* 44 (± 12.97) *RFA* 45.79 (± 12.16)
Kubat et al, 2019[62]	Retrospective chart analysis (Turkey)	GSV, AASV *CAC* 11.6 (2.5) *HLS* 11.7 (2.1) *EVLA 980 nm* 11.9 (2) *RFA* 11.7 (2) *RFA* 11.5 (2.1)	79	*HLS* 94 *EVLA 980 nm* 151 *EVLA 1470 nm* 109 *RFA* 264	C2: 59.5 C3: 29.1 C4: 7.6 C5: 17.7	*HLS* C2: 55.8 C3: 33.7 C4: 7 C5: 3.5 *EVLA 980 nm* C2: 58.1 C3: 27 C4: 12.2 C5: 4.7 *EVLA 1470 nm* C2: 63.2	50.6 (11.68)	*HLS* 49.6 (13) *EVLA 980 nm* 48.8 (10.4) *EVLA 1470 nm* 47.4 (11.4) *RFA* 49.5 (11.4)

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, %		Age, Mean (SD), Y	
			CAC	Comparator(s)	CAC	Comparator(s)	CAC	Comparator(s)
						C3: 25.7 C4: 6.4 C5: 4.6 *RFA* C2: 57 C3: 27.7 C4: 12.9 C5: 2.4		
Compared With RFA and HLS								
Ay et al, 2020	Prospective Comparative Cohort (Turkey)	GSV *CAC* 7.9 (1.6) *RFA* 7.6 (1.6) *HLS* 8.1 (2.0)	85	*RFA* 70 *HLS* 62	C2–4: 78.8 C5–6: 21.1	*RFA* C2–4: 81.4 C5–6: 18.5 *HLS* C2–4: 77.4 C5–6: 22.5	40.0 (13.1)	*RFA* 38.2 (11.7) *HLS* 37.8 (12.8)
Compared With RFA and EVLA								
Eroglu and Yasim, 2018[65]	RCT (Turkey)	GSV, SSV[a] *CAC* 7.6 (1.9) *RFA* 7.8 (1.9) *EVLA* 8.0 (1.9)	168	*RFA* 149 *EVLA* 139	C2: 2.4 C3: 55.4 C4: 42.3[b] C5: 0[b] C6: 0[b]	*RFA* C2: 1.3 C3: 57.7 C4: 38.3 C5: 2 C6: 0.7 *EVLA* C2: 2.9 C3: 55.4 C4: 41.7 C5: 0 C6: 0	47.7 (11.9)	*RFA* 44.9 (10.5) *EVLA* 45.9 (10.4)

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, %		Age, Mean (SD), Y	
			CAC	Comparator(s)	CAC	Comparator(s)	CAC	Comparator(s)
Compared With EVLA								
McGuinness et al, 2019[67]	Retrospective chart analysis (Canada)	GSV *CAC* 9.3 (2.1) *EVLA* 9.3 (2.2)	62	57	NR	NR	MD 49 (IQR 44–62)	MD 53 (IQR 43–65)
Koramaz et al, 2017[68]	Retrospective chart analysis (Turkey)	GSV *CAC* 6.88 (1.8) *EVLA* 7.15 (1.77)	150	189	C2: 13.3 C3: 44 C4: 36 C5: 6.7	C2: 11.6 C3: 49.2 C4: 33.9 C5: 5.3	45.09 (12)	47.08 (11)
Bozkurt and Yilmaz, 2016[48]	Prospective Comparative Cohort (Turkey)	GSV *CAC* 7.2 (1.8) *EVLA* 7.1 (1.6)	154 Hispanic 4% Nonwhite 6%	156 Hispanic 8% Nonwhite 8%	C2: 67.5 C3: 24.7 C4a: 5.8 C4b: 1.9	C2: 76.3 C3: 21.2 C4a: 1.3 C4b: 1.3	42.5 (13.1)	40.2 (11.2)
Compared With RFA								
VeClose[69-72,81]	RCT (United States)	GSV *CAC* 4.9 (range 0–9) *RFA* 5.1 (range 2.4–11)	108	114	C2: 57 C3: 30 C4a: 12 C4b: 2	C2: 56 C3: 32 C4a: 11 C4b: 2	49 (range 26.6–70.6)	50.5 (range 25.6–70.1)
Ovali and Sevin, 2019[71, 2019 #77]	Prospective comparative cohort (Turkey)	GSV *CAC* 7.0 (4.23) *RFA* 7.2 (2.31)	116	128	C2–C4: 102 C4–C6: 14	C2–C4: 115 C4–C6: 13	49.21 (13.1)	47.3 (13.75)
Yang et al, 2019[63]	Retrospective chart analysis (Canada)	GSV, SSV, AASV, PV Mean diameter NR	148	317	C2:39 C3: 28 C4a: 22 C4b: 5 C5: 1	C2: 53 C3: 21 C4a: 21 C4b: 3 C5: 1	57 (1)	57 (1)

Author, Year	Study Design, (Country)	Vein(s) Treated, Mean Diameter, mm (± SD)	Sample Size, N		CVI Severity, CEAP C Class, %		Age, Mean (SD), Y	
			CAC	Comparator(s)	CAC	Comparator(s)	CAC	Comparator(s)
Bademci et al, 2019[64]	Prospective comparative cohort (Turkey)	GSV[c] *CAC* MD 7 (min 5.5, max 9) *RFA* MD 7.25 (min 5.5, max 9.5)	75	84	C2: 65.3 C3: 25.3 C4: 9.3[d]	C2: 64.3 C3: 23.8 C4: 11.9	46.33 (14.4)	48.09 (13.25)

Abbreviations: AASV, anterior accessory saphenous vein; CAC, cyanoacrylate adhesive closure; CEAP, Clinical-Etiologic-Anatomic-Pathophysiologic classification; CVI, chronic venous insufficiency; EVLA, endovenous laser ablation; GSV, great saphenous vein; HLS, high ligation and stripping; IQR, interquartile range; MA, meta-analysis; MD, median; NR, not reported; PV, perforator vein; RCT, randomized controlled trial; RFA, radiofrequency ablation; SSV, small saphenous vein; Y, years.

[a]Significant difference in the vessels treated, with more SSV treated in EVLA group (P = .003).[65]

[b]C4, 5, 6 combined in statistical analyses.[65]

[c]Isolated GSV insufficiency.[64]

[d]C1,5,6 excluded.[64]

Vein Closure

CAC VERSUS RFA

One RCT[72,81] and four nonrandomized studies[63,64,66,92] assessed vein closure after CAC or RFA (Table 16). The nonrandomized studies reported that the proportion of veins completely closed with CAC was very high (94.7% to 100%) at all follow-up times and not statistically significantly different at any time from the vein closure in the RFA group (92.8% to 100% at various follow-up times; see Table 16).

The VeClose RCT was a large multicentre trial designed to establish the noninferiority of CAC compared with RFA.[69-72,81] The study initially followed patients having either procedure for 36 months and then was extended to 5 years. The trial defined a noninferiority margin of 10% for CAC compared with RFA. The trial found GSV closure after CAC to be noninferior at all follow-up time points through 5 years (Table 16). The study reported that the RFA group had a numerically lower rate of freedom from recanalization over 36 months compared with CAC, but the difference between groups was not statistically significant (P = .1006).[72]

Table 16: Vein Closure After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Follow-Up Time Point	Vein Closure, % (n/N)		*P* Value
		CAC	RFA	
VeClose trial[72,81] (RCT, noninferiority trial)	3 d	100 (108/108)	99.1 (113/114	.0001[a]
	1 mo	100 (105/105)	87.3 (96/110))	< .0001[a]
	3 mo	99 (103/104)	95.4 (103/108)	< .0001[a]
	6 mo	99 (100/101)	96.2 (101/105)	.0001[a]
	12 mo	96.8 (92/95)	95.9 (93/97)	.0015[a]
	24 mo	95.3 (82/86)	94.0 (79/84)	.0034[a]
	36 mo	94.4 (68/72)	91.9 (68/74)	.0050[a]
	60 mo	94.6 (44/47)	100 (33/33)	< .025[a]
Ay et al, 2020[92] (prospective comparative cohort)	1 wk	97.6 (83/85)	97.1 (68/70)	.431
	1 mo	87.1 (74/85)	91.4 (64/70)	.015
	6 mo	84.7 (72/85)	88.6 (62/70)	.007
	12 mo	82.4 (70/85)	87.1 (61/70)	.003
Ovali and Sevin, 2019[66] (prospective comparative cohort)	Post-operative	100 (128/128)	100 (116/116)	NR
	12 mo	99.5 (101/102)	96.6 (107/112)	.072
Yang et al, 2019[63] (retrospective chart analysis)	1 wk	100 (106/106)	99 (180/182)	NR
	8 wk	100 (106/106)	99 (180/182)	NR
Bademci et al, 2019[64] (prospective comparative cohort)	1 mo	100 (75/75)	98.8 (83/84)	.34
	6 mo	96 (72/75)	95.2 (80/84)	.81
	12 mo	94.7 (71/75)	92.8 (78/84)	.64

Abbreviations: CAC, cyanoacrylate adhesive closure; d, day(s); mo, month(s); n, number of people; N, total number of people in group; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation; wk, week(s).

[a]*P* value is for 10% noninferiority.

Vein closure tended to be slightly better in the CAC group compared with RFA across studies and time points. The magnitude of this increased likelihood ranged from 1% to 14% across studies; however all confidence intervals crossed 1 (no effect) (Figure 6). The absolute increases were nearly identical (Appendix A4, Figure A3).

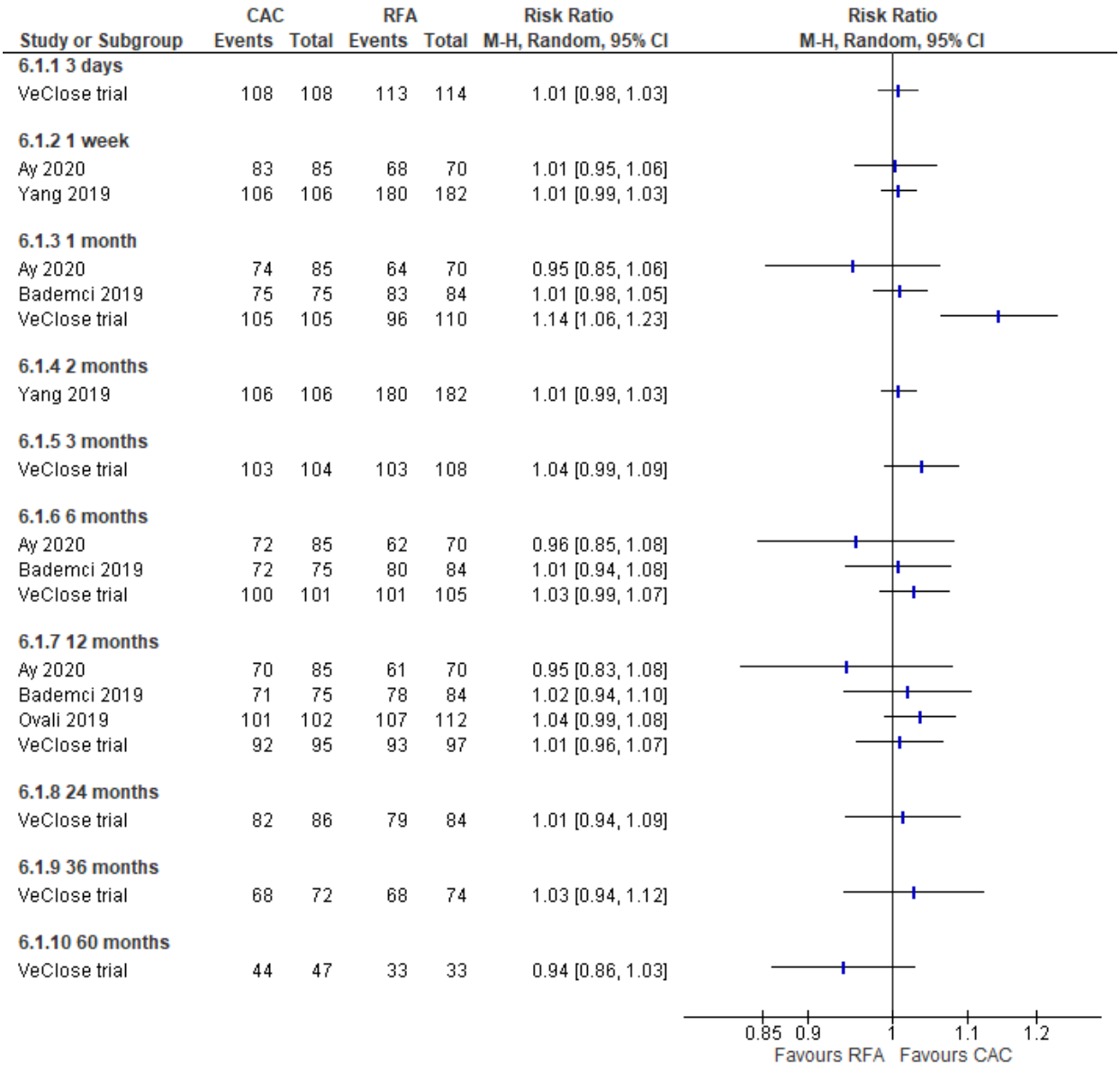

Figure 6: Vein Closure in Studies Comparing Cyanoacrylate Adhesive Closure and Radiofrequency Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; M-H, Mantel-Haenszel; RFA, radiofrequency ablation.

Data are from both randomized controlled trials and nonrandomized studies. Estimates not pooled due to presence of methodological diversity in addition to either statistical heterogeneity (6-month data) or clinical diversity (1-month, 6-month, and 12-month data).

Data sources: Ay et al, 2020[92]; Bademci et al, 2019[64]; Ovali and Sevin, 2019[66]; VeClose trial 2015-2020[69-72,81]; Yang et al, 2019.[63]

CAC VERSUS EVLA

Three nonrandomized studies compared vein closure after CAC and EVLA.[48,67,68] Both procedures closed the target veins in approximately 90% of cases or greater. There were no statistically significant differences in the proportion of veins closed with CAC or EVLA (Table 17), with the exception of one study that found greater closure with CAC at 1-month follow-up;[48] however, there was no longer a difference at 6-month or 12-month assessment.[48]

Table 17: Vein Closure After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Author, Year (Study Design)	Follow-Up Time Point	Vein Closure, % (n/N)		*P* Value
		CAC	EVLA	
McGuiness et al, 2019[67] (comparative cohort)	Post-operative DUS	89.5[a] (55/62)[a]	91.8[a] (52/57)[a]	.60
Koramaz et al, 2017[68] (retrospective chart analysis)	12 mo	98.6 (148/150)	97.3 (184/189)	.659
Bozkurt and Yilmaz, 2016[48] (prospective comparative cohort)	3 d	100 (154/154)	97.4 (152/156)	NR
	1 mo	96.7 (148/153)	87.1 (135/155)	< .001
	6 mo	96.6 (141/146)	91.7 (133/145)	.127
	12 mo	95.8 (136/142)	92.2 (130/141)	.138

Abbreviations: CAC, cyanoacrylate adhesive closure; d, day(s); DUS, duplex ultrasound; EVLA, endovenous laser ablation; mo, month(s); n, number of people; N, number of people in group; NR, not reported.

[a]Proportion reported as per study results, and number of vein closures calculated by subtracting number of anatomic failures from Table II in McGuiness et al.[67]

Vein closure (total occlusion) was similar between CAC and EVLA across studies and time points (relative risk of closure ranged from 11% better to 3% worse across time). A potential trend toward better closure with CAC was seen in one study[48] in the early follow-up period (Figure 7). However, confidence intervals at nearly all time points cross 1, indicating we cannot exclude no effect. Absolute risk differences (increase) in vein closure were comparable (Appendix 4, Figure A4).

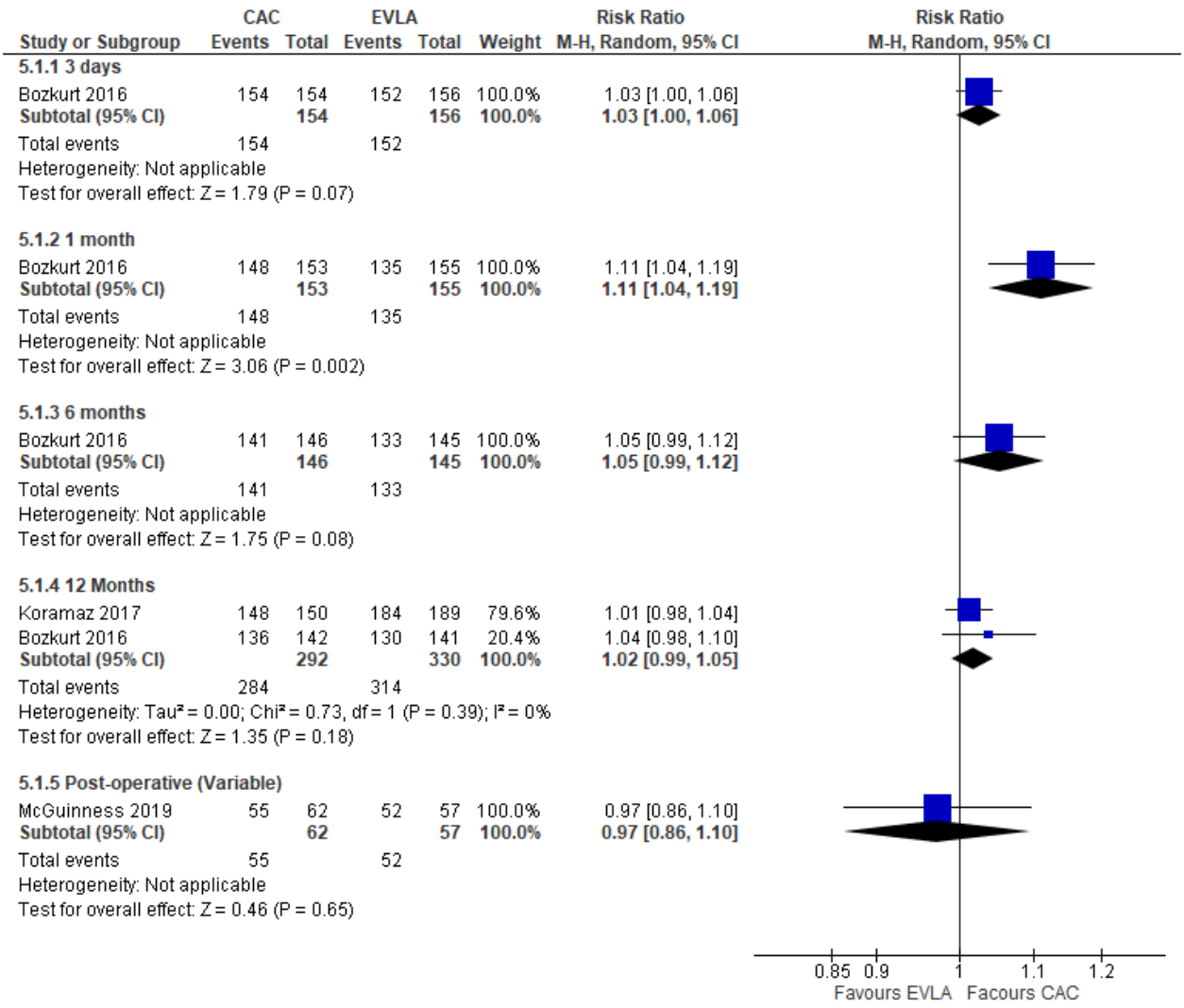

Figure 7: Vein Closure in Studies Comparing Cyanoacrylate Adhesive Closure and Endovenous Laser Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel.

Events are instances of complete vein closure. Statistical heterogeneity was not an issue; however, a random effects model was used in our meta-analysis to account for differences in disease severity between the studies by Bozkurt and Yilmaz[48] and Koramaz et al.[68]

Data sources: Bozkurt and Yilmaz, 2016[48]; Koramaz et al, 2017.[68]

CAC VERSUS EVLA AND RFA

One RCT[65] and one nonrandomized study[62] compared CAC with multiple alternative treatments. The RCT by Eroglu and Yasim[65] examined vein closure 6, 12, and 24 months after CAC, RFA, or EVLA and found no statistically significant difference between the three groups ($P > .05$). Closure rates were above 90% at all time points in all groups and ranged from 90.5% to 98.1% (Table 18).

Kubat et al[62] compared outcomes of five interventions used to treat a population with extremely dilated veins (diameter ≥ 10 mm): surgical vein stripping, CAC, RFA, and two variations of EVLA (1470 nm and 980 nm wavelengths). For vein closure, only the endovenous procedures were compared because surgery physically removes the vein. The study found a statistically significant difference between CAC, RFA, and the two variations of EVLA at both 6- and 12-month follow-up; the CAC group had a lower proportion of closed veins (89.9% at 6 months, 84.8% at 12 months). People who underwent 980-nm EVLA also had a lower proportion of closed veins (93.4% at 6 months, 88.1% at 12 months) compared with RFA or 1740-nm EVLA.[62] All results for this outcome are in Table 18.

Table 18: Vein Closure After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation or Radiofrequency Ablation

Author, Year (Study Design)	Follow-Up Time Point	Vein Closure, % (n/N)			*P* Value
		CAC	EVLA	RFA	
Kubat et al, 2019[62] (Retrospective chart analysis)	6 mo	89.9 (71/79)	*1470 nm* 96.3 (105/109) *980 nm* 93.4 (141/151)	98.9 (261/264)	.001
	12 mo	84.8 (67/79)	*1470 nm* 95.4 (104/109) *980 nm* 88.1 (133/151)	95.8 (253/264)	.001
Eroglu and Yasim, 2018[65] (RCT)	6 mo	98.1	95.1	94.1	Between groups > .05
	12 mo	94.7[b]	94.2	92.5	
	24 mo	92.6[b]	91.5	90.9	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; mo, month(s); RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]Statistically significant difference at $P < .05$.

[b]Statistically significant change within groups from 6 to 24 mo ($P < .005$).[65]

We rated the quality of the evidence for vein closure after CAC compared with RFA as moderate, rating down for imprecision (Appendix 2, Table A7), moderate compared with EVLA, downgrading for imprecision (Table A8), and very low compared with thermal ablation or surgical vein stripping for people with vein diameter of 10 mm or more, downgraded for indirectness (Table A9).

Procedure Failure and Recanalization

The VeClose trial[72,81] reported that some people experienced partial recanalization of the GSV but all remained asymptomatic up to 5 years of follow-up. Kaplan-Meier freedom from recanalization analysis demonstrated noninferiority of CAC (91.4%) versus RFA (85.2%) through 60-month follow-up, with no new recanalization documented between 36 and 60 months ($P < .025$).[81] Table 19 presents results for procedure failure and partial or complete recanalization of the treated vein after CAC compared with RFA, EVLA, and surgical vein stripping in 10 studies.

Table 19: Procedure Failure, Recanalization, and Retreatment After Cyanoacrylate Adhesive Closure Ablation, Thermal Ablation, or Surgical Vein Stripping

Author, Year (Study Design)	Follow-Up Time Point	Procedure Failure, % (n)	Partial or Complete Recanalization, % (n/N)		Reintervention, % (n)
			CAC	Comparator(s)	
VeClose trial[72,81,a] (RCT, noninferiority trial)		NR		*RFA*	NR
	1 mo[a]		0 (0/105)	9.1 (14/110)	
	3 mo[a]		0.9 (1/104)	4.6 (5/108)	
	6 mo[a]		1.0 (1/101)	3.8 (4/105)	
	12 mo[a]		3.2 (3/95)	4.1 (4/97)	
	24 mo[a]		4.6 (4/86)	6.0 (5/84)	
	36 mo[a]		5.5 (4/72)	8.1 (6/74)	
	60 mo		No new recanalization since 36 mo		
Ay et al, 2020[92] (prospective comparative cohort)		NR		*RFA*	NR
	1 wk[b]		2.4 (2/85)	2.9 (2/70)	
	1 mo[b]		12.9 (11/85)	8.9 (6/70)	
	6 mo[b]		15.3 (13/85)	11.4 (8/70)	
	12 mo[b]		17.6 (15/85)	12.9 (9/70)	
Ovali and Sevin, 2019[66] (prospective comparative cohort)	12 mo	NR	Partial, < 1 (1/102)	*RFA* Partial, 4.5 (5/112)[b]	NR
Kubat et al, 2019[62] (retrospective study)		NR	Overall recurrence: 8.3%		NR
	6 mo		10.1 (8/79)	*RFA* 1.1 (3/264) *EVLA 1470 nm* 3.7 (4/109) *EVLA 980 nm* 6.6 (10/151)	
	12 mo	NR	15.2 (12/79)	*RFA* 5.7 (15/264) *EVLA 1470 nm* 5.5 (6/109) *EVLA 980 nm* 14.6 (22/151) *HLS* 3.2 (3/86)[c]	

Author, Year (Study Design)	Follow-Up Time Point	Procedure Failure, % (n)	Partial or Complete Recanalization, % (n/N)		Reintervention, % (n)
			CAC	Comparator(s)	
Yang et al, 2019[63] (retrospective chart analysis)		NR		*RFA*	HLS (1) Conservative treatment (1)
	1 wk		(0/106)	1 (2/182)	
	8 wk		(0/106)	1 (2/182)	
McGuiness et al, 2019[67] (comparative cohort)	Post-operative	*CAC* 10.5 (6) *EVLA* 8.2 (4) *P* =.60	1 recanalization w/o reflux in each group		*CAC* 3.2 (2/62) *EVLA* 3.5 (3/57)
Bademci et al, 2019[64] (prospective comparative cohort)		NR		*RFA*	
	1 mo		0 (0/75)	1.2 (1/84)	> .05
	6 mo		4 (3/75)	4.8 (4/84)	> .05
	12 mo		5.3 (4/75)	7.2 (6/84)	> .05
Eroglu and Yasim, 2018[65] (RCT)	6 mo[d]	NR	1.9 (NC)	*RFA* 5.9 (NC) *EVLA* 4.9 (NC)	NR
	12 mo[d]		5.3 (NC)	*RFA* 7.5 (NC) *EVLA* 5.8 (NC)	
	24 mo[d]		7.4 (NC)	*RFA* 9.1 (NC) *EVLA* 8.5 (NC)	
Koramaz et al, 2017[68] (retrospective chart analysis)	6 and 12 mo	NR	1.3 (2/150)	*EVLA* 2.6 (5/189)	NR
Bozkurt and Yilmaz, 2016[48,e] (prospective comparative cohort)		NR		*EVLA*	NR
	3 d		0 (0/154)	2.5 (4/156)	
	1 mo		3.3 (5/153)	26.8 (20/155)	
	6 mo		3.5 (5/146)	8.3 (12/145)	
	12 mo		4.2 (6/142)	7.8 (11/141)	

Abbreviations: CAC, cyanoacrylate adhesive closure; d, day; EVLA, endovenous laser ablation; HLS, high ligation and stripping; mo, month(s); NC, not calculable; NR, not reported; RFA, radiofrequency ablation; wk, week(s); w/o, without.

[a]Recanalizations at all time points up to and including 36 mo calculated from Table 2 of Morrison et al, 2019,[72] due to that article's comprehensiveness and noted corrections to the data in earlier publications.

[b]Calculated as remaining proportion from values on vein closure in our Table 16 above.

[c]Recurrent cases in HLS group include 2 neovascularization, 1 perforator vein insufficiency.[62]

[d]Calculated as remaining proportion from values on vein closure in our Table 18 above.

[e]Incidence rates for partial recanalization and total at 1, 6, and 12 months also reported separately in Bozkurt and Yilmaz[48] (p. 110, "Closure Data" and Table 3).

Across studies and follow-up times, the odds of recanalization (complete or partial) were generally lower after CAC treatment relative to RFA (Figures 8a and 8b) or EVLA (Figures 9a and 9b).

Compared with RFA, the odds of recanalization favouring CAC ranged from 0.77 to 0.03 (Figure 8a). There is uncertainty around these results with wide confidence intervals that cross 1 in most cases. These odds correspond with an increased (absolute) risk of recanalization with RFA of approximately 1% to 4% (Figure 8b). Also, one study had results in the opposite direction, favouring RFA.[62] These outlier

results may be attributed to markedly different clinical characteristics of the study population (see footnote, Figure 8b).

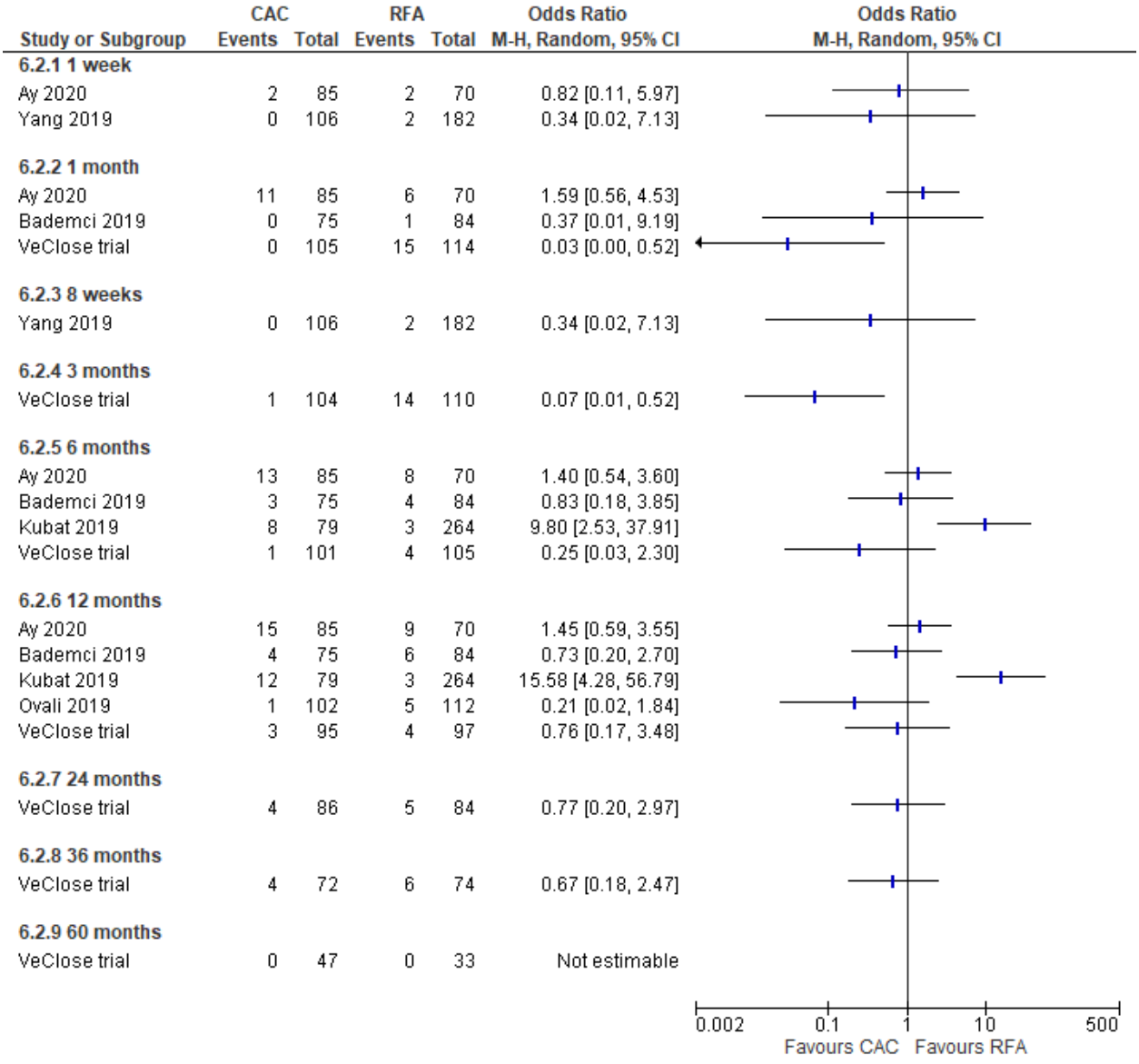

Figure 8a: Odds of Complete or Partial Recanalization After Cyanoacrylate Adhesive Closure or Radiofrequency Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; M-H, Mantel-Haenszel; RFA, radiofrequency ablation.

Events are instances of partial or complete recanalization. Data are from both randomized controlled trials and nonrandomized studies. Estimates not pooled due to presence of methodological and clinical heterogeneity. Kubat et al[62] included only patients with extremely large (≥ 10 mm) diameter veins.

Data sources: Ay et al, 2020[92]; Bademci et al, 2019[64]; Kubat et al, 2019[62]; Morrison et al, 2019 and 2020[72,81] (VeClose trial); Ovali and Sevin, 2019[66]; Yang et al, 2019.[63]

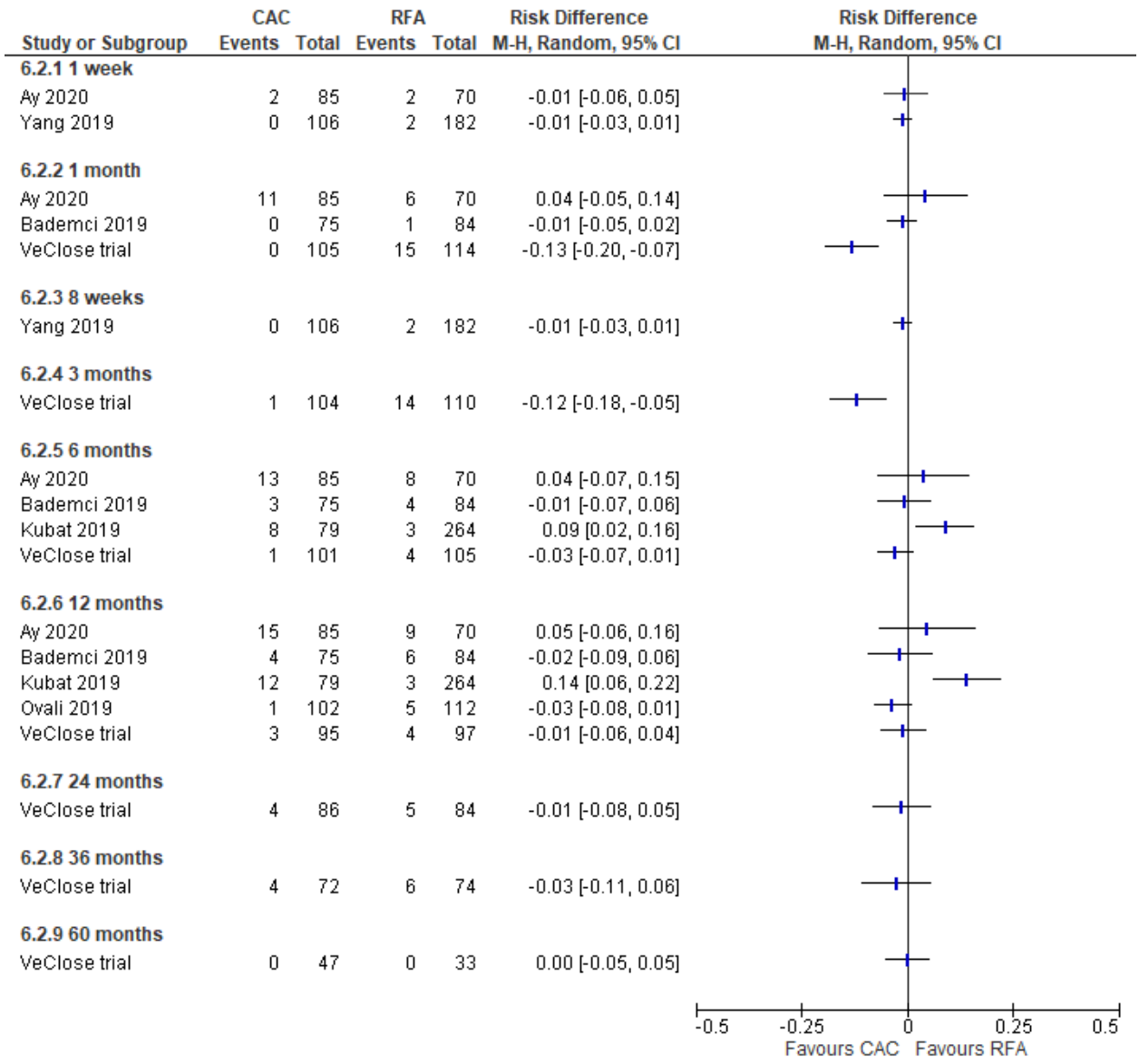

Figure 8b: Absolute Risk of Complete or Partial Recanalization After Cyanoacrylate Adhesive Closure or Radiofrequency Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; M-H, Mantel-Haenszel; RFA, radiofrequency ablation.

Events are instances of partial or complete recanalization. Data are from both randomized controlled trials and nonrandomized studies. Estimates not pooled due to presence of methodological and clinical heterogeneity. Kubat et al[62] included only patients with extremely large (≥ 10 mm) diameter veins.

Data sources: Ay et al, 2020[92]; Bademci et al, 2019[64]; Kubat et al, 2019[62]; Morrison et al, 2019 and 2020[72,81] (VeClose trial); Ovali and Sevin, 2019[66]; Yang et al, 2019.[63]

Results were similar in the comparison with EVLA, showing slightly lower recanalization after CAC (Figures 9a and 9b). The meta-analysis showed that, at 6 months after treatment, the odds of recanalization were 0.42 for CAC compared with EVLA (95% CI 0.17–1.03). The same direction of effect was seen in the 12-month pooled estimate (odds ratio 0.51 favouring CAC, 95% CI .022–1.23). The corresponding absolute risk of recanalization was 2% to 3% higher after EVLA compared with CAC (Figure 9b). In most cases, the confidence intervals across estimates crossed the null.

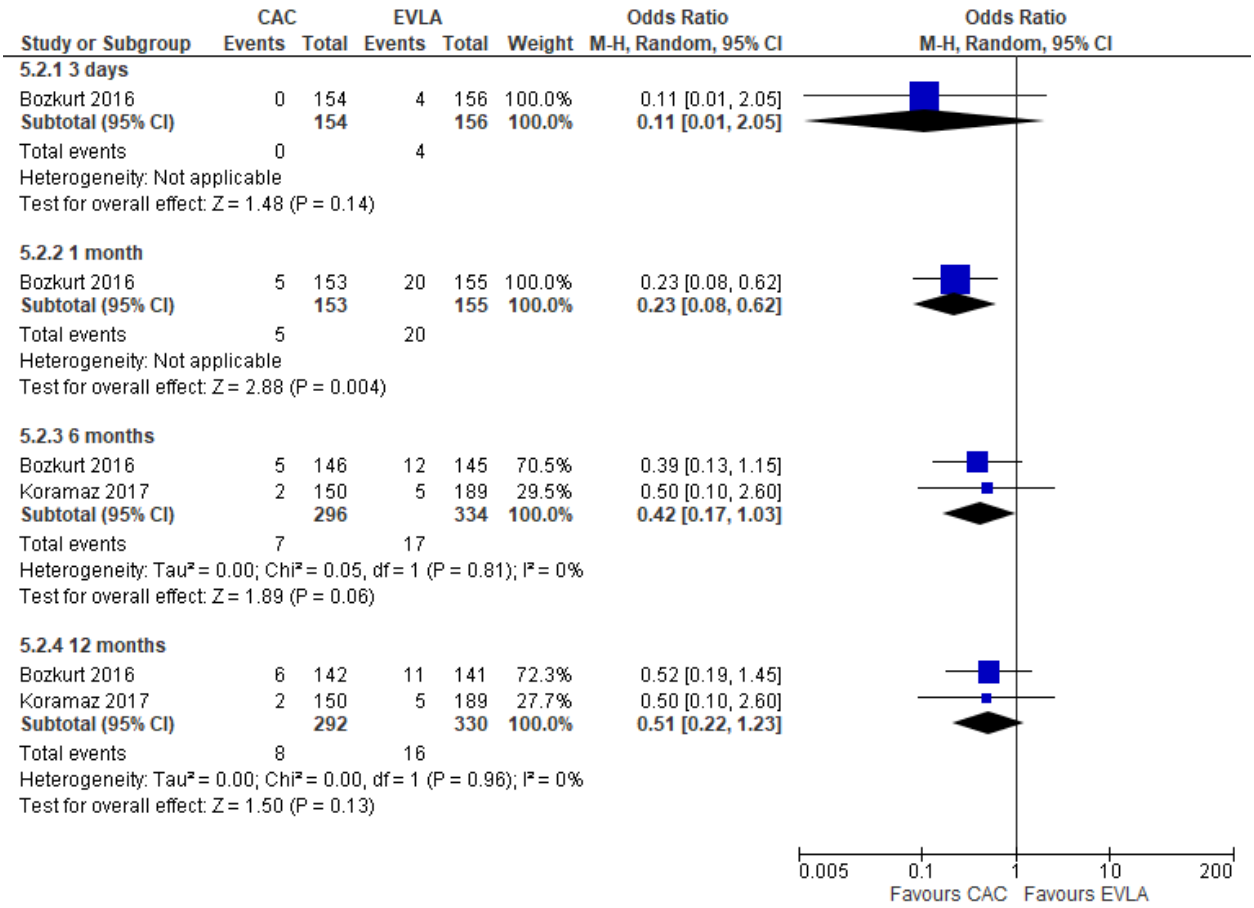

Figure 9a: Odds of Complete or Partial Recanalization After Cyanoacrylate Adhesive Closure or Endovenous Laser Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel.

Events are instances of partial or complete recanalization. Statistical heterogeneity was not an issue; however, we used a random effects model to account for differences in the distribution of disease severity between the studies by Bozkurt and Yilmaz[48] and Koramaz et al.[68]

Data sources: Bozkurt and Yilmaz, 2016[48]; Koramaz et al, 2017.[68]

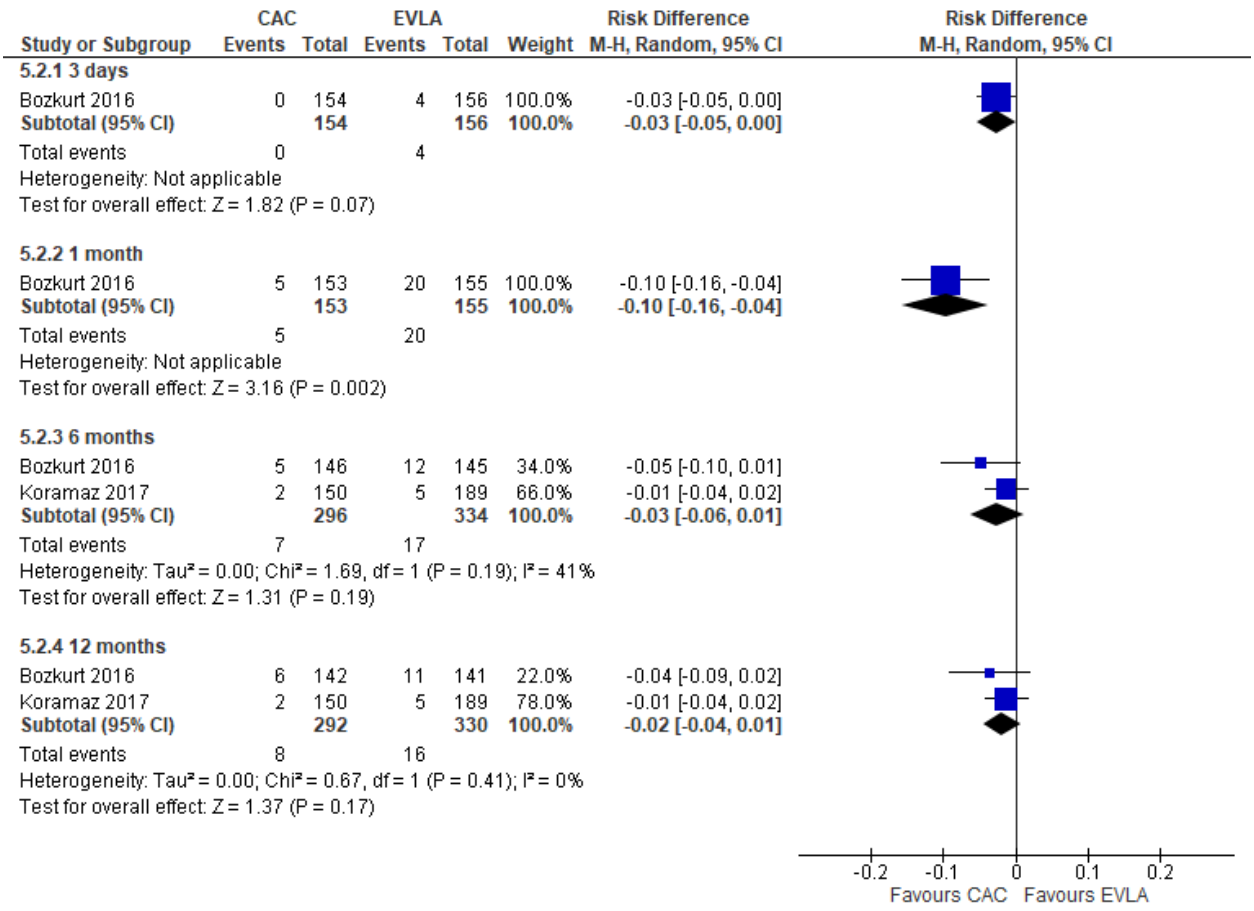

Figure 9b: Absolute Risk for Complete or Partial Recanalization After Cyanoacrylate Adhesive Closure or Endovenous Laser Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel.

Events are instances of partial or complete recanalization. Statistical heterogeneity was not an issue; however, we used a random effects model to account for differences in the distribution of disease severity between the studies by Bozkurt and Yilmaz[48] and Koramaz et al.[68]

Data sources: Bozkurt and Yilmaz, 2016[48]; Koramaz et al, 2017.[68]

We rated the quality of the evidence for recanalization after CAC compared with RFA (Appendix 2, Table A7) and EVLA (Table A8) as moderate, rating down for imprecision. We rated the body of evidence as very low compared with thermal ablation or surgical vein stripping for people with vein diameter of 10 mm or more, downgrading for indirectness (Table A9).

Change in Clinical Symptoms

All studies measured the effects of the treatments on clinical symptoms using the Venous Clinical Severity Scale (VCSS).[86]

CAC VERSUS RFA, EVLA, AND SURGICAL VEIN STRIPPING

One study compared five interventions for GSV insufficiency where vein diameter before treatment was 10 mm or greater. Clinical symptoms after CAC, RFA, EVLA (980 nm or 1470 nm), or high ligation and stripping were evaluated at baseline and 1 year, and compared between groups.[62] The mean VCSS scores were similar at baseline (*P* = .489). After all the treatments, there was improvement in VCSS from baseline (*P* < .001),[62] but no difference between the groups in the improvement at 1 year.[62] Exact figures are presented in Table 20.

Table 20: Venous Clinical Severity Score After Cyanoacrylate Adhesive Closure vs. Thermal Ablation or Surgical Vein Stripping for Great Saphenous Vein Insufficiency With Vein Diameter ≥ 10 mm

Author, Year (Study Design)	Intervention	Baseline VCSS, Mean (SD)	1 Year VCSS, Mean (SD)	*P* Value[a]
Kubat et al, 2019[62] (retrospective study)	CAC	6.0 (1.6)	1.4 (1.5)	.531
	RFA	5.9 (1.6)	1.4 (1.4)	
	EVLA 1470 nm	5.5 (1.1)	1.1 (1.2)	
	EVLA 980 nm	5.7 (1.7)	1.6 (1.8)	
	HLS	5.9 (1.7)	1.2 (1.2)	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; HLS, high ligation and stripping; RFA, radiofrequency ablation; SD, standard deviation; VCSS, Venous Clinical Severity Score.

[a]*P* value is for between-group differences at follow-up.

CAC VERSUS RFA AND SURGICAL VEIN STRIPPING

One prospective observational study compared VCSS at 1 year after surgical vein stripping (high ligation and stripping, HLS), radiofrequency ablation, and cyanoacrylate adhesive.[92] There were no differences in baseline VCSS scores between groups (CAC mean 9.11 ± 4.98, RFA 9.33 ± 4.37, and HLS 8.63 ±3.95, *P* = .71). All groups had improvement compared with baseline after treatment (*P* < .001).

However, at 1-year follow-up, surgical vein stripping resulted in lower (better) VCSS scores compared with CAC (*P* <.001). Mean VCSS scores at follow-up were HLS 3.05 (±1.76), RFA 4.07 (±2.69) and CAC 4.89 (±3.2), respectively. Potential reasons for this difference and the importance of this finding from a single study are uncertain.

CAC VERSUS RFA AND EVLA

Eroglu and Yasim[65] simultaneously analyzed VCSS scores between groups assigned to receive CAC, RFA, or EVLA with an analysis of variance. Scores were similar at baseline and improved within groups at the 6-month follow-up (*P* < .001), with the improvement persisting to the subsequent 1-year and 2-year follow-up times (Table 21). Between treatment groups, the CAC groups had significantly lower scores than both other groups at 6-month and 2-year follow-up (*P* not reported).[65] At 1 year, all three groups differed from one another (*P* not reported).

Table 21: Venous Clinical Severity Score After Cyanoacrylate Adhesive Closure vs. Thermal Ablation

Author, Year (Study Design)	Baseline VCSS, MN			Follow-Up Time Point	Follow-Up VCSS, MN			*P* Value
	CAC	EVLA	RFA		CAC	EVLA	RFA	
Eroglu and Yasim, 2018[65] (RCT)	7.8[a]	7.6[a]	7.7[a]	6 mo	4.1[a]	4.6[a]	4.8[a]	Sig (NR)
				1 y	3[a]	3.6[a]	3.8[a]	Sig (NR)
				2 y	2.7[a]	3.5[a]	3.7[a]	Sig (NR)

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; mo, month(s); MN, mean; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation; Sig, statistically significant at $P < .05$; VCSS, Venous Clinical Severity Score; y, year(s).

[a]Values extracted by visual inspection of Figure 3 in Eroglu and Yasim.[65]

CAC VERSUS EVLA

Table 22 summarizes the results of the two relevant studies, both of which reported similar improvements in VCSS score for CAC and EVLA.[48,68] Koramaz et al[68] compared VCSS 1 year after CAC or EVLA. Scores were comparable between groups at baseline ($P = .483$) and improved after treatment within each group compared with baseline ($P < .001$). Bozkurt and Yilmaz[48] also compared the VCSS after two interventions; however, they did so at multiple follow-up times (1 month, 6 months, and 1 year). Consistent with Koramaz et al, VCSS scores improved within groups ($P < .001$), but there was no difference between CAC and EVLA.

Table 22: Venous Clinical Severity Score After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Author, Year (Study Design)	Baseline VCSS, MN (SD)		Follow-Up Time Point	Follow-Up VCSS, MN (SD)		*P* Value
	CAC	EVLA		CAC	EVLA	
Koramaz et al, 2017[68] (Retrospective chart analysis)	7.53 (1.03)[a]	7.73 (1.58)[a]	1 y	2.79 (1.05)[a]	2.83 (1.21)[a]	.882
Bozkurt and Yilmaz, 2016[48] (Prospective comparative cohort)	5.7 (2.3)[b]	5.7 (1.2)[b]	1 mo	2.4 (0.9)[b]	2.2 (0.7)[b]	.997[c]
			6 mo	1.3 (0.9)[b]	1.2 (0.6)[b]	
			1 y	0.6 (0.7)[b]	0.7 (0.5)[b]	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; mo, month(s); MN, mean; SD, standard deviation; VCSS, Venous Clinical Severity Score; y, year.

[a]Median score and range also provided. CAC and EVLA groups both had baseline median scores of 7 (ranges 7–13). Follow-up median scores: CAC 2 (range 1–6), EVLA 2 (range 2–6).[68]

[b]Different group sizes at each follow-up point were noted. CAC n = 154 at baseline, 153 at 1 mo, 145 at 6 mo, and 142 at 1 y. EVLA had n = 156 at baseline, 155 at 1 mo, 145 at 6 mo, and 141 at 1 y.[48]

[c]Between groups comparisons at multiple time points analyzed with repeated-measures analysis of variance.[48]

CAC VERSUS RFA

Two nonrandomized studies[64,66] and the VeClose trial[69-72,81] compared VCSS of patients treated with CAC or RFA. Across these studies, follow-up tended to be between 1 and 12 months, but the VeClose trial followed patients up to 60 months after treatment (Table 23). Baseline scores did not differ between intervention groups, and improvement was seen within each group in all studies.

At every follow-up time across studies, including through to 3 years and 5 years after treatment, improvements in VCSS scores were comparable between CAC and RFA (Table 23).

Table 23: Venous Clinical Severity Score After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Baseline VCSS, MN (SD)[a]		Follow-Up Time Point	Follow-Up VCSS, MN (SD)[a]		*P* Value
	CAC	RFA		CAC	RFA	
VeClose trial[70,72,81] (RCT, noninferiority trial)	5.5 (2.6)	5.6 (2.6)	3 d[70]	4.9 (1.3)	5.0 (1.9)	.60[b]
			1 mo[70]	2.3 (1.7)	2.6 (2.0)	
			3 mo[70]	1.9 (1.6)	2.0 (2.0)	
			6 mo[72,c]	1.5[b,c] (1.8[b,c])	1.6[b,c] (1.9[b,c])	.5694
			12 mo[72,c]	1.4 (1.8[b,c])	1.5 (1.9[b,c])	
			24 mo[72,c]	1.3[b,c] (1.8[b,c])	1.6[b,c] (2.0[b,c])	NR
			36 mo[72,c]	1.2[b,c] (1.7[b,c])	1.7[b,c] (2.4[b,c])	NS (NR)
			60 mo[81]	1.3 (SE 0.2)	1.4 (SE 0.3)	0.6927
Ovali and Sevin, 2019[66] (Prospective comparative cohort)	5.75 (1.23)	5.79 (1.19)	12 mo	1.03 (0.96)	1.11 (0.94)	.921
Bademci et al, 2019[64] (Prospective comparative cohort)	MD 7 (r: 4–14)	MD 8 (r: 5–14)	1 mo	MD 3 (r: 2–6)	MD 3 (r: 2–6)	.06
			6 mo	MD 2 (r: 1–5)	MD 2 (r: 1–5)	.19
			12 mo	MD 1 (r: 1–4)	MD 1 (r: 1–4)	.72

Abbreviations: CAC, cyanoacrylate adhesive closure; d, day; MD, median; mo, month(s); MN, mean; NR, not reported; NS, not significant; r, range (min–max); RCT, randomized controlled trial; RFA, radiofrequency ablation; SD, standard deviation; SE, standard error; VCSS, Venous Clinical Severity Score.

[a]Unless otherwise stated.

[b]*P* value is for repeated measures ANOVA (baseline, 3 d, 1 mo, 3 mo).[70]

[c]Values approximated and/or calculated from data presented in figures in Morrison et al, 2019[72] using WebPlotDigitizer software.[43]

In the VeClose trial, it was reported that during the first 12 months of follow-up VCSS decreased rapidly and equally in both groups (*P* = .5694).[71] In general in the study, VCSS scores were comparable over time, with no differences between groups, and the maximum symptom improvement was seen at

6 months and persisted into 24 months[69] and 36 months.[72] Interestingly, there was no difference in the mean VCSS change from baseline in patients with complete closure compared to those without.[81] In the 5-year extension of the VeClose trial, the study authors noted that VCSS improved 75% from baseline within the CAC group, 72% in the RFA group (within-groups *P* <.0001).[81]

In addition, the VeClose trial reported notable changes in patients' CEAP classification at 5-year follow-up.[81] Among people undergoing CAC, 41.1% (23/56) experienced a reduction of at least 2 classes (less severe venous disease) compared to their baseline severity. Specifically, 66.7% of those originally classified as C3 (10/15, combined roll-in and randomized) have improved to C0 or C1 by 5-year follow-up, while 16.7% (1/6 combined roll-in and randomized) of C4a or C4b are now C0, C1, or C2.[81] In the RFA group, 39.4% of treatments (13/33) resulted in changes of at least 2 classes lower versus baseline. The authors note that 50% of C3 (5/10) patients are now C0 or C1, and 75% (3/4) of people classified at baseline as C4a or C4b are now C0, C1, or C2.[81] No formal comparisons between treatment groups were made for these changes in CEAP classification.

We rated the quality of the evidence for change in clinical symptoms after CAC as moderate compared with RFA (Appendix 2, Table A7) and EVLA (Table A8), rating down for imprecision. We rated the body of evidence as very low compared with thermal ablation and surgical vein stripping for people with vein diameter of 10 mm or more, downgrading for indirectness (Table A9). The body of evidence for change in clinical symptoms comparing CAC and surgical vein stripping was rated as very low due to risk of bias and indirectness (Table A10).

Quality of Life

CAC VERSUS EVLA

Bozkurt and Yilmaz[48] compared disease-specific quality of life between people who were treated with either CAC or EVLA. The Aberdeen Varicose Vein Questionnaire was administered at baseline and at three time points after treatment. Lower scores (range 0 to 100) reflect better quality of life. They found improvement within groups (*P* < .001) but no differences between groups at 1-, 6-, or 12-month follow-up (Table 24).[48] The authors suggest a trend toward slightly better AVVQ scores in the CAC group based on their data.

Table 24: Quality of Life Score After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Author, Year (Study Design)	Baseline, Mean AVVQ (SD)		Follow-Up Time Point	Follow-Up, Mean AVVQ (SD)		*P* Value
	CAC	EVLA		CAC	EVLA	
Bozkurt and Yilmaz, 2016[48] (Prospective comparative cohort)	18.1 (5.0)	18.8 (4.6)	1 mo	7.5 (2.1)	7.9 (2)	.062[a]
			6 mo	4.6 (1.4)	4.9 (1.3)	
			1 y	4.6 (1.4)	4.9 (1.3)	

Abbreviations: AVVQ, Aberdeen Varicose Vein Questionnaire score; CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; mo, month; SD, standard deviation; y, year.

[a]Between-groups comparisons at multiple time points analyzed with repeated-measures ANOVA, with a trend toward better quality of life (lower scores) in the CAC group.

CAC VERSUS RFA

Three studies compared disease-specific quality of life after either RFA or CAC, also using the Aberdeen Varicose Vein Questionnaire.[64,66,81] In all three studies, baseline scores were comparable between groups, and each group had significant improvement at follow-up compared with their baseline scores. All studies followed patients to at least 12 months post-procedure and, as noted above, the VeClose trial followed up for the longest duration after treatment, up to 60 months. The VeClose authors reported that, during the initial 12 months, AVVQ scores decreased rapidly and equally in both treatment groups (P = .5536)[71] and that, upon reflection across 36 months, the maximum improvement was seen at 6 months and persisted to 36 months.[72] At 60 months, AVVQ scores had improved within groups from baseline by 55% in the CAC group and 67% in people who had received RFA (P < .0001).[81]

Between treatment groups, there were no differences in the improvement in quality of life found at any time point in any study (Table 25).

Table 25: Quality of Life Score After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Baseline Score, MN (SD)[a]		Follow-Up Time Point	Follow-Up Score, MN (SD)[a]		*P* Value
	CAC	RFA		CAC	RFA	
Disease-Specific Quality of Life: Aberdeen Varicose Vein Questionnaire						
VeClose trial[70-72,81] (RCT, noninferiority trial)	18.9 (9.0)	19.4 (9.9)	1 mo[70]	11.9 (7.1)	12.6 (8.3)	0.53[b]
			3 mo[70]	11.6 (7.5)	10.7 (8.6)	
			6 mo[72]	10.2[c](5.6[c])	9.1[c] (7.1[c])	NS (NR)
			12 mo[72]	9.7[c] (7.1[c])	8.4[c] (6.5[c])	NS (NR)
			24 mo[72]	8.2[c] (7.9[c])	8.3[c] (7.5[c])	NS (NR)
			36 mo[72]	7.3[c] (6.4[c])	8.2[c] (7.8[c])	NS (NR)
			60 mo[81]	8.3 (9.6[d])	6.6 (5.7[d])	.3418
Ovali and Sevin, 2019[66] (prospective comparative cohort)	17.43 (6.38)	18.21 (6.93)	12 mo	4.93 (1.56)	5.13 (1.49)	.752
Bademci et al, 2019[64] (prospective comparative cohort)	MD 17 (range 15–21)	17 (11–21)	1 mo 6 mo 12 mo	7 (6–9) 5 (4–7) 4 (3–6)	8 (5–13) 6 (3–10) 4 (1–9)	.10 .84 .61
Generic Quality of Life: EQ-5D TTO						
VeClose trial[70,81] (RCT, noninferiority trial)	0.935 (.113)	0.918 (.116)	1 mo[70] 3 mo[70]	0.965 (.113) .965 (.095)	0.961 (.106) .965 (.083)	.34[b]
			60 mo[81]	0.97 (.08)	.94 (.11)	NR

Abbreviations: CAC, cyanoacrylate adhesive closure; EQ-5D TTO, EuroQol 5-Dimension Time Trade Off; MD, median; MN, mean; mo, month(s); NR, not reported; NS, not significant; RCT, randomized controlled trial; RFA, radiofrequency ablation; SD, standard deviation.

[a]Unless otherwise noted values are mean and standard deviation.

[b]Repeated-measures ANOVA comparing baseline, 1 mo, and 3 mo.[70]

[c]Values approximated and/or calculated from data presented in figures in Morrison et al, 2019[72] using WebPlotDigitizer software.[43]

[d]Standard deviation calculated from data presented in Figure 3 of Morrison et al, 2020[81] using WebPlotDigitizer software.[43]

In addition to the AVVQ, the VeClose trial also administered the EQ-5D quality of life survey, time trade-off utility scores (Table 25), and its 100-point "health thermometer" visual analogue scale (VAS). At baseline, there was no difference between the CAC and RFA groups (*P* = .29). By 3-month follow-up, the EQ-5D index scores improved within each group compared with baseline by approximately 0.3 units; however, there were no differences between treatment groups (Table 25).[70] Over the first 12 months of follow-up, the authors described that EQ-5D index scores for overall quality of life increased by small and similar amounts in both groups (*P* = .1645).[71] By month 24, EQ-5D scores were reported to have improved over time, but again with no between-groups differences.[69] The index scores were depressed at baseline and had improved at month 60 by 15% in the CAC group and 12% in the RFA group, which differed compared with baseline (*P* < .0001) but not between groups (*P* not reported). After CAC, almost all people followed to 60 months had improved in the domains of pain/discomfort, mobility, and usual activities.

According to the EQ-5D VAS, no differences between groups were found in the sustained improvement in quality of life over 36 months of observation,[72] and people's overall quality of life after CAC improved from baseline at 60 months by 22% (*P* = .236), whereas with RFA it improved by 15% from baseline (*P* = .079).[81]

We rated the quality of the evidence for quality of life after CAC compared with RFA as moderate, rating down for imprecision (Appendix 2, Table A7), and low compared with EVLA (Table A8).

CAC VERSUS RFA AND SURGICAL VEIN STRIPPING

Ay et al[92] assessed quality of life using both the SF-36 and the disease-specific Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ-14) in their prospective nonrandomized study of outcomes following CAC compared with RFA and high ligation and stripping (HLS) vein surgery. The CIVIQ-14 has been validated and measures pain, physical status, and psychological status over 14 items.[93] On both instruments, scores range from 0 to 100 with higher scores indicating better quality of life. There was improvement within each group on both CIVIQ-14 and SF-36 at 12-month follow-up compared with baseline (*P* < .001).[92]

Baseline CIVIQ-14 mean scores differed significantly between the CAC and HLS groups (82.8, standard deviation [SD] 6.4 vs. 85.8, SD 6.1, *P* =.02). The mean baseline score for RFA was 83.8 (SD 6.4) which did not differ from the other groups. Each group differed at follow-up: HLS had the highest score (mean 96.5, SD 3.0), followed by RFA (94.6, SD 3.6) and CAC (91.6, SD 5.8, *P* < .001).

Scores for several of the SF-36 dimensions did not differ between any of the groups at baseline. However, physical functioning differed between the HLS and CAC groups at baseline (mean 77.5, SD 14.8, vs. 68.1, SD 17.1, *P* < .001). Social functioning differed between HLS and RFA at baseline as well (mean 75.4, SD 13.1, vs. 69.4, SD 13.7, *P* = .04). At follow-up, between the CAC and HLS groups, scores for the subdomains of energy/fatigue, emotional well-being, pain, and health change were higher (better) for HLS (*P* < .05 for all subdomains). Both HLS and RFA had higher scores than CAC on physical functioning, role limitations due to emotional problems, and social functioning (*P* < .05 for all subdomains). No differences between groups were found at follow-up on scores reflecting role limitations due to physical health or for the general health subdomains of the SF-36.

Patient Satisfaction

Two studies evaluated patients' satisfaction with either CAC or thermal ablation procedures. Patient satisfaction measurement varied and was poorly described in both studies, and one study measured satisfaction differently over the 5 years of follow-up.

CAC VERSUS EVLA

Eroglu and Yasim[65] randomly assigned study participants to either CAC or EVLA procedures. Satisfaction was high in both groups, as assessed by including parameters such as freedom from pain during and after the procedure, complications, time to return to work, and change in VCSS after treatment.

CAC VERSUS RFA

The VeClose trial assessed satisfaction with either CAC or RFA at the time of the procedure and 2, 3, and 5 years after treatment.[69,72,81] Patients were asked to report if they were very satisfied, somewhat satisfied, somewhat dissatisfied, or very dissatisfied. At all time points, the vast majority of patients were either very or somewhat satisfied with their procedure, with no differences between treatment groups in the proportion of satisfied patients (Table 26). At 36 months, the trial authors report that "both groups were 'somewhat satisfied' to a similar extent" (data not shown).[72]

In addition to categorizing satisfaction level, the VeClose investigators solicited from participants information about whether they "would not", "might", or "definitely would" hypothetically have the same treatment again.[81] The proportion of responses were similar at all time points. At the time of the index procedure, 89.4% in the CAC group and 93.9% of the RFA group said they "definitely would" have the procedure again (P = .466). At 24 months, the proportion of people responding "definitely would" was 82.6% (71/86) in the CAC group and 77.4% (65/84) in the RFA group (P not reported[69]) and, at 60 months, the proportion responding "definitely would" was 93.6% in the CAC group and 87.9% in the RFA group (P = .374).[81]

Table 26: Patient Satisfaction After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Measure of Satisfaction	Time Point, Responses	n/N (%) CAC	n/N (%) RFA	*P* Value
VeClose trial[69,72,81] (RCT, noninferiority trial)	% participants satisfied	*At time of procedure*[81]			.921
		Very satisfied	43/47 (91.5)	30/33 (90.9)	
		Somewhat satisfied	3/47 (6.4)	2/33 (6.1)	
		Somewhat dissatisfied	1/47 (2.1)	1/33 (3.0)	
		Very dissatisfied	0	0	
		24 mo[69]			NR
		Very satisfied	68/86 (79.1)	63/84 (75)	
		Somewhat satisfied	8/86 (9.3)	19/84 (22.6)	
		36 mo[72]			.30
		Very satisfied	61/72 (84.7)	58/74 (78.4)	
		Somewhat satisfied	Similar[a]	Similar[a]	
		60 mo[81]			.340
		Very satisfied	43/47 (91.5)	28/33 (84.8)	
		Somewhat satisfied	4/47 (8.54)	4/33 (12.1)	
		Somewhat dissatisfied	0	1/33 (3.0)	
		Very dissatisfied	0	0	

Abbreviations: CAC, cyanoacrylate adhesive closure; mo, month(s); n, number of people; N, number of people in group; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]Reported that groups were "somewhat satisfied" to a similar extent; data not reported.[72]

We rated the quality of the evidence for patient satisfaction after CAC as low compared with RFA (Appendix 2, Table A7), rating down for risk of bias and imprecision, and as low compared with EVLA (Table A8).

Recovery Time

CAC VERSUS RFA AND EVLA

A randomized trial by Eroglu and Yasim[65] compared the proportion of people taking off 1, 2, 3, 4, or more days from work following varicose vein treatment with CAC, RFA, or EVLA. An analysis of variance found that all the interventions differed from each other and a significant proportion of people in the CAC group took less time off (only 1 or 2 days) compared with both RFA and EVLA (Table 27).

Table 27: Recovery Time After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation or Radiofrequency Ablation

Author, Year (Study Design)	No. Days Off Work	n (%)			*P* Value
		CAC	EVLA	RFA	
Eroglu and Yasim, 2018[65] (RCT)	1	161 (95.8)	105 (75.5)	70 (50.3)	< .001
	2	7 (4.2)	24 (17.3)	53 (35.6)	
	3	0	10 (7.2)	20 (13.4)	
	4+	0	0	1 (0.7)	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; No, number; RFA, radiofrequency ablation.

We rated the quality of the evidence as low for recovery time after CAC compared with RFA (Appendix 2, Table A7) and EVLA (Table A8).

Complications

The reporting of major and minor complications after CAC varied substantially across studies and was largely descriptive with rare between-groups statistical testing. Major and minor complications are reported here by comparison, as the interventions examined differed notably across studies.

CAC VERSUS RFA, EVLA, OR SURGICAL VEIN STRIPPING

Kubat et al[62] compared complications in five procedures: CAC, RFA, 1470-nm EVLA, 980-nm EVLA, and surgery (high ligation and stripping). Study participants had to have a vein diameter of at least 10 mm before treatment. In the CAC group, the authors reported that there was no thrombophlebitis, but a "phlebitis-like reaction" to the adhesive was observed in 5 people (8%). No major complications including skin burns, DVT, pulmonary embolism, or surgical site infections were noted for the comparators.[62]

For minor complications, the CAC group had less (no) ecchymosis (bruising) compared with the other interventions ($P = .02$), and hyperpigmentation was most common after 980-nm EVLA ($P < .01$).[62] There was no difference between groups other than those noted above ($P > .05$) and for paresthesia (Table 28).

Table 28: Minor Complications After Cyanoacrylate Adhesive Closure vs. Thermal Ablation or Surgical Vein Stripping in Patients With Vein Diameter ≥ 10 mm

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	Comparator(s)	
Kubat et al, 2019[62] (Retrospective chart analysis)	Ecchymosis	0	*RFA* 11 (4.2%) *EVLA 1470 nm* 6 (5.5) *EVLA 980 nm* 14 (9.3) *HLS* 9 (9.6)	.02
	Paresthesia[a]	0	*RFA* 1 (0.4) *EVLA 1470 nm* 1 (0.9) *EVLA 980 nm* 3 (2) *HLS* 2 (2.1)	.34
	Hyperpigmentation	0	*RFA* 7 (2.) *EVLA 1470 nm* 4 (3.7) *EVLA 980 nm* 17 (11.3) *HLS* 2 (2.1)	<.01

Abbreviations: CAC, cyanoacrylate adhesive closure; HLS, high ligation and stripping; EVLA, endovenous laser ablation; RFA, radiofrequency ablation.

[a]Post-operative paresthesia resolved in all patients by the end of 3 weeks.

CAC VERSUS RFA OR SURGICAL VEIN STRIPPING

Comparing CAC with RFA or high ligation and stripping (HLS) vein surgery, one study found more phlebitis-like reaction in the CAC group (P = .002), and more ecchymosis after HLS (P = .001).[92] Overall, complication rates between CAC and RFA for any complication were similar while patients undergoing HLS were more likely to have any complication (P = .016) (Table 29).[92]

Table 29: Complications After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation or Surgical Vein Stripping

Author, Year (Study Design)	Complication	n (%)			*P* Value
		CAC	RFA	HLS	
Ay et al, 2020[92] (prospective comparative cohort)	DVT	0	0	1 (1.6)	.29
	Paresthesia	1 (1.1)	1 (1.4)	2 (3.2)	.63
	Ecchymosis	3 (3.5)	2 (2.8)	15 (24.2)	.001
	Access site wound complications	0	1 (1.4)	3 (4.8)	.34
	Phlebitis	2 (2.3)	3 (4.2)	4 (6.4)	.48
	Phlebitis-like reaction	8 (9.4)	0	0	.002
	Skin pigmentation	2 (2.3)	2 (2.8)	2 (3.2)	.95
	Any complication	15 (17.6)	9 (12.9)	20 (32.3)	.016

Abbreviations: CAC, cyanoacrylate adhesive closure; DVT, deep vein thrombosis; HLS, high ligation and stripping; EVLA, endovenous laser therapy; RFA, radiofrequency ablation.

CAC VERSUS THERMAL ABLATION

Eroglu and Yasim[65] documented complications following CAC and both thermal endovenous procedures (EVLA and RFA) (Table 30). There was no difference between groups in the frequency of DVT, phlebitis, or bleeding at entry site. Ecchymosis (bruising) was more common in the RFA group (18.1%) versus EVLA (4.3%) or CAC (5.4%, $P < .001$).[65]

Table 30: Complications After Cyanoacrylate Adhesive Closure vs. Thermal Ablation

Author, Year (Study Design)	Complication	Severity	n (%)			*P* Value
			CAC	RFA	EVLA	
Eroglu and Yasim, 2018[65] (RCT)	DVT	Major	0	1 (0.7)[a]	0	.36
	Bleeding at entry site	Minor	0	2 (1.3)	0	.13
	Phlebitis	Minor	11 (6.5)	19 (12.8)	13 (9.3)	.17
	Ecchymosis	Minor	9 (5.4)	27 (18.1)	6 (4.3)	< .001[b]

Abbreviations: CAC, cyanoacrylate adhesive closure; DVT, deep vein thrombosis; EVLA, endovenous laser ablation; RFA, radiofrequency ablation.

[a]DVT was observed extending to the external iliac vein of 1 patient who was hospitalized and treated with low molecular-weight heparin for 5 days and dabigatran after discharge.

[b]More common in RFA group.

CAC VERSUS EVLA

Three studies compared complications after EVLA and CAC.[48,67,68] Table 31 presents major complications reported in those studies; minor complications are in Table 32.

Table 31: Major Complications After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	EVLA	
McGuiness et al, 2019[67] (Comparative cohort)	Neovascularization	0	0	NR
	DVT from GSV	0	0	NR
	Popliteal DVT	0	1 (1.7%)	NR
Koramaz et al, 2017[68] (Retrospective chart analysis)	DVT	0	3 (1.6%)[a]	.258
	Burns	0	4 (2.1%)	.133

Abbreviations: CAC, cyanoacrylate adhesive closure; DVT, deep vein thrombosis; EVLA, endovenous laser ablation; GSV, great saphenous vein; NR, not reported.

[a]DVTs all endovenous heat-induced class I, treated with low molecular-weight heparin and dissolved in 7–15 days (mean 10 days).[68]

In the study by Koramaz et al,[68] there was more pigmentation and phlebitis after EVLA compared with CAC. In the study by Bozkurt and Yilmaz,[48] the rates for these complications were numerically higher for EVLA but no differences were found statistically. There was a trend toward more bruising following EVLA in Koramaz et al,[68] whereas Bozkurt and Yilmaz[48] found a statistically significant difference in the same direction ($P < .001$). There was numerically more paresthesia in the EVLA group in both studies, with 1 study noting a statistical difference.[48] Ecchymosis was markedly lower in the CAC group in the study by Bozkurt and Yilmaz[48] (Table 32).

Bozkurt and Yilmaz[48] categorized ecchymosis by the percentage of bruising along the treated vein segment (< 25, 25–50, 50–75, > 75) and paresthesia by temporary or permanent (Table 32). In this study, skin pigmentation decreased to almost invisible over 1 year of follow-up.[48]

Table 32: Minor Complications After Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	EVLA	
Koramaz et al, 2017[68] (retrospective chart analysis)	Pain (1st week)	7 (4.7)[a]	17 (9)[b]	.123
	Pigmentation	0	11 (5.9)[c]	.002
	Bruising	0	5 (2.6)[c]	.069
	Paresthesia	0	3 (1.6)	.258
	Phlebitis	3 (2.1)[d]	15 (7.9)[e]	.015
Bozkurt and Yilmaz, 2016[48] (prospective comparative cohort)	Phlebitis	7 (4.5)	12 (7.7)	.248
	Ecchymosis	22 (14)	73 (47)	< .001
	Skin pigmentation	2 (1.3)	3 (1.9)	1
	Paresthesia	0	7 (4.5)[f]	.015

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation.

[a]Pain resolved during first 3 days.[68]

[b]Pain resolved within 4–7 days.[68]

[c]Burns, pigmentation, and bruising were resolved by 6 months.[68]

[d]Patients with phlebitis fully recovered in 3–5 days (median 4).[68]

[e]Phlebitis resolved with 14-day treatment with antibiotics/NSAIDs.[68]

[f]Includes temporary (n = 5) and permanent (n = 2) paresthesia.[48]

CAC VERSUS RFA

Major complications were rare across studies comparing CAC and RFA[63,64,66,69-72,81] (Table 33). Bademci et al 2019[64] reported none of the patients in their study experienced major complications including death, DVT, or pulmonary embolism. In the VeClose trial, no patients in either group experienced device- or procedure-related complications, DVT, or pulmonary embolism.[70] At 3 months, a total of 78 adverse events overall occurred in 63 people (34 people who had CAC, 29 people who had RFA); 69% of people who underwent CAC and 75% of people treated with RFA had zero adverse events. There was no difference in the number (0–4; *P* = .37) or severity (mild, moderate, severe; *P* = .35) of events between the CAC and RFA groups within the first 3 months of follow-up.[70] Between month 12 and 60, no major complications occurred in either group.[69,72,81]

Table 33: Major Complications After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	RFA	
VeClose trial[70,71] (RCT, noninferiority trial)	*0–3 mo*[70]			
	DVT	0	0	NR
	PE	0	0	NR
	Severe AE	2 (2)[a]	1 (1)[a]	NR
	3–12 mo[71]			
	Thrombus extension	0	2[b]	NR
Ovali and Sevin, 2019[66] (prospective comparative cohort)	Skin burn	0	1 (< 1)	.339
	DVT	0	0	NA
Yang et al, 2019[63] (retrospective chart analysis)	Superficial phlebitis	4/106 (4)	28/182 (15)	< .05
	Paresthesia	3 (3)[c]	5 (3)[d]	NR
	DVT	1 (1)[e]	1 (1)[e]	NR
	Access site issues	3 (3)[g]	1 (1)[f]	NR

Abbreviations: AE, adverse event; CAC, cyanoacrylate adhesive closure; DVT, deep vein thrombosis; mo, month(s); NA, not applicable; NR, not reported; PE, pulmonary embolism; RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]One case each of breast cancer, kidney stones, and symptomatic orthostatic hypertension. Authors do not note which everts occurred in which group, and all were deemed unrelated to procedure/device.[70]

[b]Moderate severity, 1 DVT in non-index leg, and 1 endovenous heat-induced thrombosis. Resolved without sequelae.[71]

[c]All cases were resolved by 8 weeks.[63]

[d]All cases persisted at 8 weeks but were not debilitating.[63]

[e]DVTs were clinically asymptomatic and treated with a course of anticoagulant.[63]

[f]Wound persisted at 8 weeks and required debridement.[63]

[g]Subcutaneous infection and a painful lump at site due to foreign body response. All lumps were removed under local anesthetic. No one became systemically ill, 1 person was also put on antibiotics, and all healed without issue.[63]

Table 34 presents the minor complications reported in four studies comparing CAC and RFA. Bademci et al[64] observed no paresthesia in the CAC group and 1 case in the in RFA group, which was a statistically significant difference ($P < .02$). However, there was no difference in the frequency of phlebitis, skin pigmentation, or ecchymosis. Similarly, Ovali and Sevin[66] observed more complications and side effects in the RFA group but the frequency did not differ statistically significantly ($P > .05$). Severe pain, ecchymosis, and sensitivity were more common in the RFA group ($P < .05$).[66]

In the VeClose trial, there was significantly less ecchymosis at day 3 following CAC procedures than in the RFA group ($P < .01$ Table 34). The type and number of complications were similar between groups ($P = .37$).[70] The total number of device-related events was similar between groups (RFA 7 events, CAC 13 events, $P = .16$). Between months 3 and 12, there were 38 adverse events, most of which were phlebitis in untreated areas or miscellaneous events deemed unrelated to the procedure.[71] The events considered "possibly" or "definitely" related to the treatment or device are in Tables 33 and 34. Between months 12 and 24, none of the 12 adverse events in 8 patients were determined to be related to the procedure or device.[69] Seven nonserious adverse events in 7 people occurred between the

24-month and 36-month follow-up. By 60 months, there were no granulomatous reactions (delayed hypersensitivity reactions).[81]

Table 34: Minor Complications After Cyanoacrylate Adhesive Closure vs. Radiofrequency Ablation

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	RFA	
VeClose trial[69-72] (RCT)	*During/after procedure*[70]	1 (< 1)	2 (1.7)	NR
	Light-headedness	0	1 (< 1)	NR
	Nausea	0	1 (< 1)	NR
	Vasovagal symptoms	MN 2.2	MN 2.4	.11
	Pain (intraprocedural)	35 (32)	71 (62)	< .01
	Day 3 ecchymosis			
	3 mo[70]			
	Phlebitis, any	22 (20)	16 (14)	> .05
	Access site burn	0	1 (1)	1.0
	Access site infection	1 (1)	1 (1)	1.0
	Paresthesia	3 (2.8)	4 (3.5)	> .05
	Superficial thrombophlebitis	3 (3)	4 (4)	.72
	Stocking irritation	2 (2)	3 (3)	1.0
	Other, not related	10 (9)	11 (10)	1.0
	3–12 mo[71, a]	Chronic phlebitis, 1 (1) Pain in medial thigh, 1 (1)	No minor complications	NR NR
	12–24 mo[69]			
	Events deemed related to procedure or device	0	0	—
	Unknown if related	Shin splints, 1 (1.1) Thigh erythema, 1 (1.1)	—	—
	24–36 mo[72]	Late-onset phlebitis, 1[b] Cystic mass in index leg, 1 Acute ankle pain, 1 Scar, 1[b] Calf pain, 1[b]	Non–treatment-zone phlebitis, 1 Superficial phlebitis, 1	NR
Ovali and Sevin, 2019[66] (prospective comparative cohort)	Thrombophlebitis	2 (1.7)	4 (3.1)	.685
	Cellulite	2 (1.7)	3 (2.3)	.998
	Paresthesia	0	3 (2.3)	.240
	Urinary retention	0	3 (2.3)	.240
	Severe pain	5 (4.3)	16 (12.5)	.042

Author, Year (Study Design)	Complication	n (%)		*P* Value
		CAC	RFA	
	Ecchymosis	12 (10.3)	26 (20.3)	.044
	Sensitivity	14 (12.1)	28 (21.9)	.038
	Induration	4 (3.5)	7 (5.5)	.645
	Edema	1 (0.9)	3 (2.3)	.360
	Pigmentation increase	2 (1.7)	4 (3.1)	.685
	Hematoma	0	1 (0.8)	.339
Yang et al, 2019[63] (retrospective chart analysis)	Superficial phlebitis	4/106 (4)	28/182 (15)	< .05
	Paresthesia	3 (3)[c]	5 (3)[c]	NR
Bademci et al, 2019[64] (prospective comparative cohort)	Phlebitis	4 (5.3)[d]	5 (6)[d]	> .05
	Skin pigmentation	2 (2.7)	3 (3.6)	> .05
	Ecchymosis	2 (2.7)	3 (3.6)	> .05
	Paresthesia	0	1 (1.2)[e]	< .02

Abbreviations: CAC, cyanoacrylate adhesive closure; MN, mean; mo, month(s); NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]Events deemed possibly or definitely related to the procedure or device. Proportion calculated with denominator of those participants evaluated at 12 months as per CONSORT diagram.[71]

[b]Events deemed to have unknown, possible, or definite relationship to the procedure or device.[72]

[c]In RFA group all persisted at 8 weeks but were not debilitating. In CAC group all resolved by 8 weeks.[63]

[d]Treated with antibiotics and nonsteroidal anti-inflammatory drugs for 1 week.[64]

[e]All spontaneously resolved by 3 months.[64]

Cyanoacrylate Adhesive Closure for Small Saphenous Vein Insufficiency Alone

CAC VERSUS RFA, EVLA, AND SURGICAL VEIN STRIPPING

The small saphenous vein runs from at or below knee (from the saphenopopliteal junction) through the lower leg in the superficial vein system.[82] A retrospective comparative study by Kubat et al,[82] published in 2020,[82] assessed outcomes of treating small saphenous vein insufficiency (SSVI) alone with five available interventions. The study used a chart review to compare outcomes of patients who underwent mainly unilateral treatment of SSVI with high ligation and vein stripping, EVLA (either 980 nm or 1470 nm), RFA, or CAC.[82] The CAC device used was VariClose (Ankara, Turkey).

The procedures were performed on 268 people (282 extremities) under spinal anesthesia (HLS, ELVA, and RFA) or local anesthesia (CAC) over approximately 5 years at two centres in Turkey. Most patients had unilateral treatment (left 54.3% or right 40.3%), and comparable baseline characteristics (age, sex, CEAP classification, vein diameter, BMI, etc.)[82] (see Table 15).

The study reported no information on the outcomes of vein closure, venous ulcer healing or recurrence, quality of life, patient satisfaction, or recovery time after treatment for SSV insufficiency alone.

Risk of Bias

Both blinding of outcome assessment and incomplete outcome data were judged to be at unclear risk of bias for the study by Kubat et al.[82] The other four domains were judged to be at low risk of bias (see Appendix 2, Table A4).

Procedure Failure and Recanalization

Success was determined by duplex ultrasonographic evidence of no distal SSV reflux and absence of neovascularization at the saphenopopliteal junction. The publication did not present the success data. The primary outcome was recurrence of varicose veins after treatment (new-onset varicose veins after the procedure). At 6 months after treatment, the rates of recurrence were comparable between groups (Table 35). However, when all interventions were compared at 12 months, recurrence was lower in the CAC, RFA, and 1470 nm EVLA groups (*P* = .005).[82]

We rated the quality of the evidence for recanalization after CAC compared with other interventions for small saphenous vein insufficiency alone as low (Appendix 2, Table A11).

Table 35: Venous Insufficiency Recurrence After Cyanoacrylate Adhesive Closure vs. Thermal Ablation or Surgical Vein Stripping for Small Saphenous Vein Insufficiency Alone

Author, Year (Study Design)	Follow-Up Time Point	Recurrence, % (n/N)				
		CAC	EVLA	HLS	RFA	*P* Value
Kubat et al, 2020[82] (retrospective chart analysis)	6 mo	7.1 (2/28)	*1470 nm* 5.6 (2/39) *980 nm* 7.7 (3/39)	11.4[a] (5/45)	3.3 (4/134)	.319
	12 mo	10.7 (3/28)	*1470 nm* 11.1 (4/39) *980 nm* 23.7 (9/39)	31.1[a] (14/45)	9.7 (13/134)	.005

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; HLS, high ligation and stripping; mo, month(s); n, number of people; N, number of people in group; RFA, radiofrequency ablation.

[a]Presence of neovascularization at saphenopopliteal junction detected on duplex ultrasound.

Change in Clinical Symptoms

Venous Clinical Severity Scores (VCSS) were similar at baseline (*P* = .493). Within groups, all patients experienced statistically significant improvement in their clinical symptoms post-treatment, as measured by the VCSS (*P* < .001).[82] There was also a statistically significant difference between the five treatments at 12-month follow-up (*P* = .025): people treated with high ligation and stripping had significantly more symptoms (higher scores) after treatment (Table 36).

Table 36: Venous Clinical Severity Score After Cyanoacrylate Adhesive Closure vs. Thermal Ablation or Surgical Vein Stripping for Small Saphenous Vein Insufficiency Alone

Author, Year (Study Design)	Procedure	Baseline VCSS, Mean (SD)	1-Year VCSS, Mean (SD)	*P* Value
Kubat et al, 2020[82] (retrospective chart analysis)	CAC	4.7 (1.3)	1.4 (1.2)	.025
	RFA	4.6 (1.4)	1.4 (1.4)	
	EVLA 1470 nm	4.5 (1.3)	1.5 (1.3)	
	EVLA 980 nm	4.3 (1.1)	1.8 (1.3)	
	HLS	4.8 (1.4)	2.2 (1.6)	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; HLS, high ligation and stripping; RFA, radiofrequency ablation; VCSS, Venous Clinical Severity Score.

We rated the quality of the evidence for change in clinical symptoms after CAC compared with other interventions for small saphenous vein insufficiency alone as low (Appendix 2, Table A11).

Complications

Kubat et al[82] reported that no major complications occurred during the study. Minor complications are summarized in Table 37. The most frequent complications were sural neuropathy (sural nerve injury), which was temporary in all but two cases (see footnote a) and ecchymosis that resolved within 2 weeks. No pigmentation, ecchymosis, or sural neuropathy occurred in the CAC group. However, thrombophlebitis was observed in two people, only in the CAC group.

Table 37: Minor Complications After Cyanoacrylate Adhesive Closure, Thermal Ablation, or Surgical Vein Stripping for Small Saphenous Vein Insufficiency Alone

		n (%)			
Author, Year (Study Design)	Procedure	Sural Neuropathy	Thrombo-phlebitis	Pigmentation	Ecchymosis
Kubat et al, 2020[82] (retrospective chart analysis)	CAC	0	2 (7.1)	0	0
	EVLA 1470 nm	5[a] (13.9)	0	3[b] (8.3)	0
	EVLA 980 nm	10 (25.6)	0	7[b] (17.9)	1 (2.6)
	RFA	12[a] (9)	0	2[b] (1.5)	0
	HLS	6 (13.5)	0	0	8 (17.8)

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; HLS, high ligation and stripping; RFA, radiofrequency ablation.

[a]All but 2 patients had neurological symptoms resolved by 6 weeks. The remaining two (1 who received 980-nm EVLA and 1 in the RFA group) experienced permanent sensory loss along the sural nerve at the end of 6 weeks.

[b]Persistent pigmentation was noted in 2 patients who received RFA, 4 who received 980-nm EVLA, and 3 who received 1470-nm EVLA.

Nonthermal Endovenous Procedures in C6 Severity Venous Disease (Subgroup Analysis)

One study assessed the effects of treating venous insufficiency in people with active venous ulcers.[78] The medical charts of patients with venous disease severity of C6 who underwent treatment with either MOCA or thermal ablation were analyzed for venous ulcer healing and time to heal. In this study, thermal ablation grouped together RFA and EVLA in all comparisons.[78] Truncal or perforator vein treatments were done between February 2012 and April 2017 at an urban hospital and medical school in New York City.

Ulcer duration and the proportion of patients having prior DVT or procedures were similar between groups. However, there were notable differences between treatment groups. Patients who received MOCA were significantly older than the thermal ablation group (mean 67.9 vs. 57.2 years, $P = .0003$), and a greater proportion of MOCA patients had multiple vein segments treated (63% vs. 16%, $P = .0010$).[78] The MOCA group had more treatment of the SSV and perforator veins ($P < .05$). The duration of venous ulcers was slightly longer in the MOCA group (mean 11.2 ± 14.4 months vs. 9.2 ± 13.9 months in the thermal ablation group, $P = .5414$).[78] The length of follow-up was longer in the thermal ablation group (mean 12.8 months, range 0–46 vs. mean 7.9 months, range 0.5–20, $P = .0220$).

At the final follow-up (46 months), 78.1% (32/41) of MOCA patients' ulcers were healed compared with 40% (10/25) in the thermal ablation group ($P = .0006$).[78] Mean time to heal in the MOCA group was numerically but not statistically significantly shorter than in the thermal group (2.26 ± 2.33 months vs. 4.43 ± 5.92 months, $P = .074$).[78] The median time to heal was 2 months for thermal ablation and 1.5 months for MOCA, and a multivariate Cox proportional hazards regression (including age and method and treatment) found that MOCA was associated with statistically higher odds of ulcer healing (odds ratio 4.65, 95% CI 2.12–10.2, $P < .001$).[78]

Occurrence of DVT after the procedure was similar between the treatment groups. Complications occurred somewhat more in the thermal ablation group (12%) than in the MOCA group (4.89%, $P = .0598$); the authors did not elaborate on the exact nature of the complications.[78] Venous ulcers reoccurred in 5.35% of patients treated with MOCA, compared with none in the thermal group, at 12.8 months follow-up ($P = .192$) Two patients in the MOCA group who experienced ulcer recurrence and one who developed pain at the site of a previous ulcer were re-treated with MOCA and healed after reintervention.

We rated the quality of the evidence for ulcer healing, time to healing, and venous ulcer recurrence after MOCA compared with thermal ablation as low (Appendix 2, Table A12).

There were no studies reporting on comparative outcomes for venous ulcer healing or recurrence after CAC.

Discussion

Our review found comparable vein closure and improvements in both venous disease symptoms and quality of life after varicose veins were treated by cyanoacrylate adhesive closure (CAC) or alternative procedures. In studies of mechanochemical ablation (MOCA), successful vein closure was lower than after thermal endovenous ablation modalities, but the thermal and MOCA procedures resulted in similar improvements in symptoms and quality of life. Change in symptoms and quality of life may be viewed as more patient-important outcomes.

Most studies did not report on recurrence and recanalization outcomes. We back-calculated recanalization from vein closure data only where the definitions of closure and recanalization were stated explicitly and clearly reciprocal. Importantly, ultrasound evidence of vein recanalization was not clearly associated with symptom persistence or warranted reintervention. Major complications were infrequent for all procedures. Minor complication rates tended to be low and similar across studies, though the nature of the complications differed somewhat.

Our findings are consistent with the published systematic reviews identified.[10,13,52-61] Though our review compares the procedures as alternatives, these comparisons are imperfect because patient characteristics, anatomy, or other circumstances influence the most appropriate treatment for a given person. For instance, tumescent anesthesia required for thermal ablation may not be well suited for an elderly person with fragile skin.

Strengths and Limitations

We excluded noncomparative studies because there are many treatment options for symptomatic varicose veins. By including nonrandomized studies, our review captured insight into the individual and comparative complication profiles of the interventions. Studies comparing nonthermal endovenous procedures with surgical vein stripping are rare, likely owing to the almost complete replacement of surgical vein stripping by thermal endovenous interventions in the past decade. Our review included two nonrandomized studies that included direct comparisons of CAC, thermal endovenous procedures, and surgical vein stripping in specific subpopulations of chronic venous insufficiency (SSVI, Kubat et al, 2020[82] and GSV with vein diameter ≥ 10 mm, Kubat et al, 2019[62]).

While nearly all studies were of people with GSV insufficiency and treatment, heterogeneity across studies in terms of design, time point of outcome measurement, and inclusion criteria precluded quantitative synthesis of most outcomes. Had we elected to conduct a network meta-analysis, evidence would have been extremely limited and restricted to RCTs, and clinical diversity and heterogeneity among data would most likely have challenged the core assumptions of network meta-analysis. The main findings from RCTs and nonrandomized studies were generally similar in both direction and magnitude despite differences in study methods, participant characteristics (e.g., spectrum of disease severity), and treatment protocols. For instance, procedural factors that may affect success for vein closure in MOCA include pullback rate (the speed with which the catheter is gradually withdrawn) and the concentrations, volumes, and type of sclerosant used.

We did not predefine interprocedural or postprocedural pain as a discrete outcome. However, we did assess clinical symptoms, quality of life, and adverse events (including pain, if reported) which may capture some of the patient experience of pain and discomfort during and after treatment. No differences were found.

Our review summarizes comparative evidence for the treatment options comprising most clinical practice in Ontario. We did not identify any published studies comparing MOCA with CAC or comparing any nonthermal endovenous procedure with less common vein-sparing procedures (e.g., ambulatory conservative hemodynamic correction of venous insufficiency—a procedure known by its French acronym, CHIVA [cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire]).

There are several subpopulations and potential effect modifiers for which it would have been valuable to better understand the effectiveness and safety of the nonthermal endovenous interventions. For

instance, while we did not specify them explicitly, it would have been of interest to compare patients with and without prior DVT, with and without significant deep vein reflux, and mild (e.g., C1–C4) versus C5 to C6 disease. The limiting factor in conducting the subgroup analyses we planned was lack of reporting of these key characteristics in the studies.

Our review examines outcomes over a lengthy duration following treatment (more than 12 months in many studies), which provides insight into short, intermediate, and longer-term effects (e.g., durability of vein closure and effects on patient-important outcomes). We did not include compression stockings or garments as a comparator, recognizing that while they can be effective in controlling symptoms of chronic venous insufficiency (e.g., edema, pain) or for preventing venous ulcer recurrence,[19] they do not resolve the underlying incompetent veins. In some jurisdictions, including Ontario, compression stockings may be trialled or required as first-line treatment. Invasive treatment may be pursued because compression stockings are not practicable (e.g., donning and doffing may be challenging for an elderly person), affordable, or adequately effective.

Ongoing Studies

We are aware of several ongoing comparative studies that have potential relevance to the research question, including one forthcoming study comparing CAC and MOCA (NCT03392753) (Table 38).

Table 38: Identified Ongoing Clinical Trials

Title	Trial Number (Registry)	Anticipated Completion of Data Collection
Randomised controlled trial of mechanochemical ablation versus cyanoacrylate adhesive for the treatment of varicose veins	NCT03392753 (ClinicalTrials.gov)	December 2019
Randomized controlled trial comparing the clinical outcomes after cyanoacrylate closure with VenaSeal Closure System and surgical stripping for incompetent saphenous veins	KCT0003203 (Clinical Research Information Service)	February 2021
Global, post-market, prospective, multi-center, randomized controlled trial of the VenaSeal™ Closure System vs. surgical stripping or endothermal ablation (ETA) for the treatment of early & advanced stage superficial venous disease	NCT03820947 (ClinicalTrials.gov)	September 2023

Conclusions

The evidence suggests that MOCA for GSV insufficiency:

- Results in slightly poorer vein closure than RFA (GRADE: Moderate) or EVLA (GRADE: Moderate)
- Slightly increases recanalization compared with RFA (GRADE: Moderate) or EVLA (GRADE: Moderate)
- Results in little to no difference in magnitude of improvement in clinical symptoms (GRADE: Moderate), quality of life (GRADE: Low), or patient satisfaction (GRADE: Moderate), compared with RFA

- Results in little to no difference in magnitude of improvement in clinical symptoms (GRADE: High), quality of life (GRADE: High), or patient satisfaction (GRADE: High), compared with EVLA
- May reduce recovery time compared with RFA (GRADE: Low) or EVLA (GRADE: Moderate)
- May facilitate greater healing of venous ulcers and similar time to healing, and similar ulcer recurrence compared with thermal ablation (GRADE: Low)

The evidence suggests that CAC for GSV insufficiency:

- Results in little to no difference in vein closure (GRADE: Moderate), recanalization (GRADE: Moderate), magnitude of improvement in clinical symptoms (GRADE: Moderate), quality of life (GRADE: Moderate), or patient satisfaction (GRADE: Low), compared with RFA
- Results in little to no difference in vein closure (GRADE: Moderate), recanalization (GRADE: Moderate), magnitude of improvement in clinical symptoms (GRADE: Moderate), quality of life (GRADE: Low), or patient satisfaction (GRADE: Low), compared with EVLA
- Likely reduces recovery time compared with RFA (GRADE: Low) or EVLA (GRADE: Low)
- May result in slightly poorer improvements in clinical symptoms or quality of life compared with surgical vein stripping; however, the evidence is very uncertain (GRADE: Very low)
- In people with GSV diameter of 10 mm or greater, may result in slightly poorer vein closure, slightly more recanalization, and comparable magnitude of improvement in clinical symptoms, compared with RFA, EVLA, and surgical vein stripping, but the evidence is very uncertain (GRADE: Very low)

The evidence suggests that CAC for SSV insufficiency:

- May result in slightly lower recanalization compared with 980 nm EVLA and surgical vein stripping, and similar recanalization as RFA and 1470 nm EVLA (GRADE: Low)
- Results in a greater magnitude of improvement in clinical symptoms compared with surgical vein stripping, and similar improvement as EVLA and RFA (GRADE: Low)

The complication profiles of both nonthermal endovenous procedures were generally minor, though the nature of adverse events differed somewhat from those following EVLA, RFA, and surgical vein stripping, as expected. Most adverse effects were mild, transient, and resolved either entirely or to a point of being a minimal interference with people's lives. However, most studies that reported complication data were not powered to statistically test differences in complications between treatment groups.

Economic Evidence

Research Question

What is the cost-effectiveness of mechanochemical ablation (MOCA) and cyanoacrylate adhesive closure (CAC) compared with other invasive procedures for people with symptomatic varicose veins?

Methods

Economic Literature Search

We performed an economic literature search on January 14, 2020, to retrieve studies published from January 1, 2012, until the search date. We set the date limit because the first in-human study of nonthermal treatments was published in 2012. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2012, and January 14, 2020
- Cost–benefit analyses, cost-effectiveness analyses, or cost–utility analyses

Exclusion Criteria

- Narrative or systematic reviews, letters/editorials, commentaries, case reports, conferences abstracts, study protocols, guidelines, and unpublished studies
- Costing studies, feasibility analyses, or cost-of-illness studies

POPULATION

Inclusion Criteria

- Adults (age 18 years and over) with symptomatic varicose veins in the great saphenous veins of the legs

Exclusion Criteria

- Varicosities in other parts of the body
- Telangiectasias (spider veins) or reticular veins

INTERVENTIONS

- Nonthermal endovenous treatments: CAC or MOCA

COMPARATORS

- Thermal endovenous treatments (e.g., endovenous laser ablation [EVLA] and radiofrequency ablation [RFA])
- Surgery (e.g., surgical vein stripping, high ligation and stripping)

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALY])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICER)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, ICERs)

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[94] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. We assessed the applicability of each study to the research question (directly, partially, or not applicable). If we found studies to be directly applicable, we would continue with assessing the limitations (minor, potentially serious, or very serious) of those studies.

Results

Economic Literature Search

The database search of the economic literature yielded 97 citations published from January 1, 2012, until January 14, 2020. We identified 20 additional studies from other sources, for a total of 87 after removing duplicates. We identified two cost–utility studies that met our inclusion criteria.[13,95] Figure 10

presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

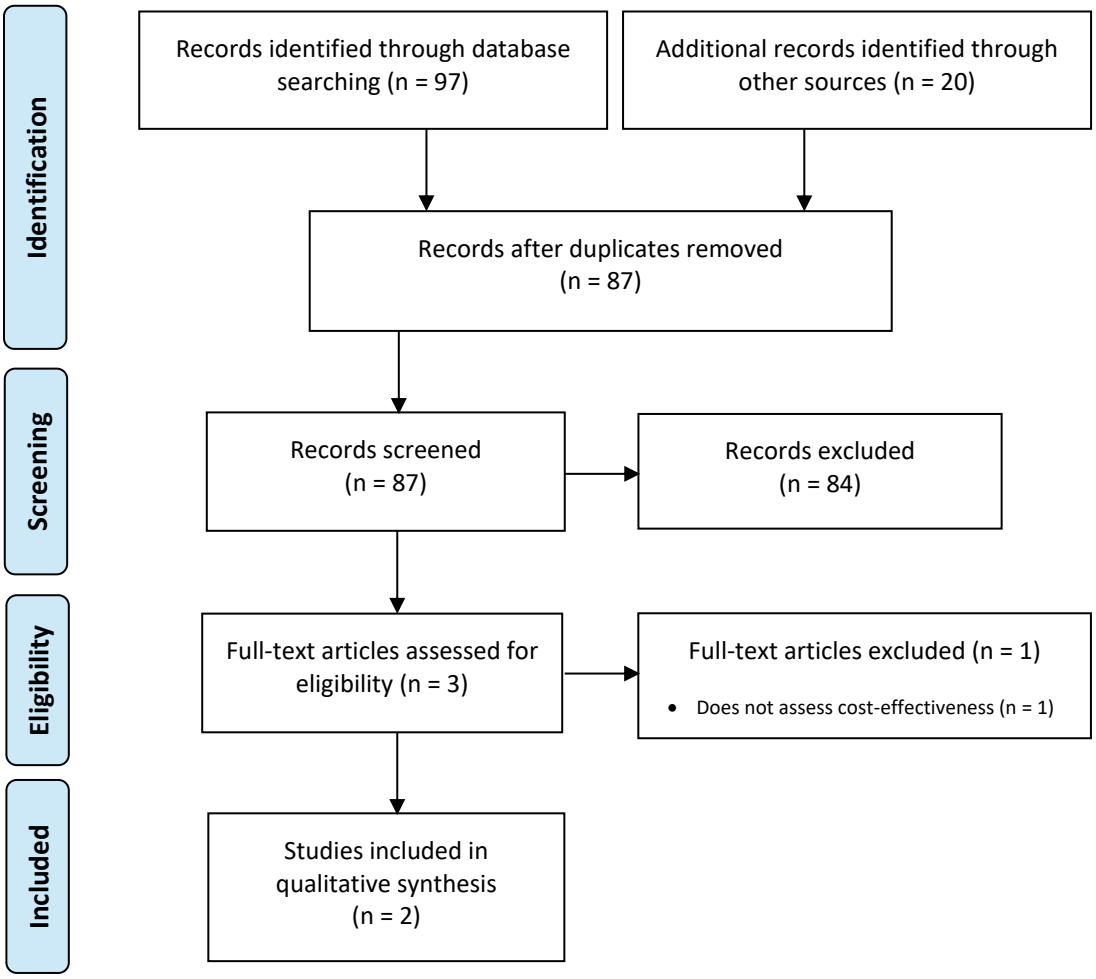

Figure 10: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[84]

Overview of Included Economic Studies

We included two cost–utility analyses[13,95] and presented their study design, populations, outcomes, time horizons, main results, and results of probabilistic analyses in Table 39. We further summarized their findings below.

Epstein et al[13] conducted a cost–utility analysis from the perspective of the UK National Health Service. The authors included conservative care (e.g., compression stockings) and six invasive treatments: surgical vein stripping (called high ligation surgery in this study), ultrasound-guided foam sclerotherapy (UGFS), ELVA, RFA, MOCA, and CAC. Conservative care was the least costly and least effective treatment option. Ultrasound-guided foam sclerotherapy was ruled out by extended dominance (i.e., the ICER for UGFS compared with conservative care [ICER: £12,071 per QALY gained] was higher than for RFA compared with UGFS [ICER: £3,491 per QALY gained]). High ligation surgery, EVLA, and CAC were dominated (more costly and less effective) by RFA. The QALYs for CAC, MOCA, high ligation surgery, EVLA, and RFA were very similar, and the difference in QALYs between any two treatments was up to 0.01 at the time horizon of 5 years. The most expensive treatment strategy was CAC (£1,395 in 5 years). The most cost-effective treatment was RFA at the willingness-to-pay value of £20,000 per QALY gained. Probabilistic analysis showed that at a willingness-to-pay of £20,000 per QALY gained, the probabilities of RFA and MOCA being cost-effective were 0.53, and 0.34, respectively.[13]

Inderhaug et al[95] conducted a cost–utility analysis from the perspectives of society and the health care payer in Norway. The societal perspective considered the loss of future productivity. This study included a no-treatment strategy and five invasive treatment strategies: surgical vein stripping (high ligation and stripping) and four endovenous treatments (EVLA, RFA, steam vein sclerosis, and CAC). The time horizon was 1 year. The costs were measured in 2015 Norwegian krone (kr) and then translated into Euros (€ 1.00 = kr 8.35). In the no-treatment strategy, the costs and QALYs were zero and 0.79, respectively. The QALYs ranged from 0.960 to 0.976 for the five invasive treatments. The most cost-effective strategy from the societal perspective was EVLA, and from the health care payer perspective it was steam vein sclerosis. The surgery was the most expensive strategy in the analysis from the societal perspective, while CAC was the most expensive from the health care payer perspective. Probabilistic analysis showed that at a willingness-to-pay amount of €59,880 per QALY gained, which was the suggested willingness-to-pay value in Norway, the probabilities of EVLA and steam vein sclerosis being cost-effective were greater than other treatments from either a societal or health care payer perspective.[95]

Table 39: Results of Economic Literature Review—Summary

Author, Year, Country	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Epstein et al, 2018[13] Spain/UK[a]	Study design: cost-utility analysis using Markov model Perspective: UK NHS Time horizon: 5 y Discount rate: 3.5%	Adults who need treatment for GSV incompetence in the upper leg	7 treatments[b]: CAC MOCA EVLA HLS RFA UGFS Conservative	QALYs CAC: 4.616 MOCA: 4.624 EVLA: 4.614 HLS: 4.614 RFA: 4.623 UGFS: 4.566 Conservative: 4.552	Currency and cost year: 2015 UK £ CAC: 1,395 MOCA: 902 EVLA: 829 HLS: 972 RFA: 808 UGFS: 609 Conservative: 440	ICER: UK £/QALY gained[c] MOCA vs. RFA: 311,101 RFA vs. conservative: 5,148 <u>Probabilistic analysis</u> At WTP of £20,000/QALY gained, the probabilities of being cost-effective were RFA 0.53, MOCA 0.34, EVLA 0.06, conservative treatment 0.06
Inderhaug et al, 2018[95] Norway	Study design: cost-utility analysis using decision tree Perspective: societal and health care payer in Norway Time horizon: 1 y Discount rate: NA	Females aged 50 y with CEAP C2 (clinical score indicating varicose veins) and GSV insufficiency	5 treatments and no treatment: CAC EVLA HLS RFA SVS No treatment	QALYs *Societal perspective*[d] CAC: 0.969 EVLA: 0.975 HLS: 0.971 RFA: 0.960 SVS: 0.976 No treatment: 0.790 *Health care payer perspective*[d] SVS: 0.975 QALYs in other strategies are same as those reported from the societal perspective	Currency and cost year: 2015 € (Euro) *Societal perspective*[d] CAC: 2,079 EVLA: 1,558 HLS: 3,506 RFA: 2,096 SVS: 1,595 No treatment: 0 *Health care payer perspective*[d] CAC: 1,627 EVLA: 788 HLS: 1,159 RFA: 1,147 SVS: 755 No treatment: 0	ICER: €/QALY gained *Societal perspective*[e] EVLA vs. no treatment: 8,448 SVS vs. EVLA: 39,258 *Health care payer perspective*[f] SVS vs. no treatment: 4,073 <u>Probabilistic analysis</u> *Societal perspective* At WTP of €59,880/QALY gained (suggested WTP in Norway[95]), the probabilities of being cost-effective were EVLA 0.45 and SVS 0.42[g] *Health care payer perspective* At WTP of €59,880/QALY gained, the probabilities of being cost-effectiveness were SVS 0.50, EVLA 0.42, HLS 0.08[g]

See notes, next page.

Notes for Table 39:
Abbreviations: CAC, cyanoacrylate adhesive closure; CEAP, clinical-etiology-anatomy-pathophysiology classification; EVLA, endovenous laser ablation; GSV, great saphenous vein; HLS, high ligation and stripping, or high ligation surgery; ICER, incremental cost-effectiveness ratio; MOCA, mechanochemical ablation; NA, not applicable; NHS, National Health Service; QALY, quality-adjusted life-year; RFA, radiofrequency ablation; SVS, steam vein sclerosis; UGFS, ultrasound-guided foam sclerotherapy; UK, United Kingdom; WTP, willingness-to-pay; y, year(s).
[a]The first author was affiliated with a university in Spain, but the costs of this study were evaluated from the perspective of the UK NHS and social care system.
[b]The study included multiple treatments. Authors did not specify which treatments were interventions, and which ones were comparators.
[c]CAC, EVLA, and HLS were dominated (more costly and less effective) by RFA. UGFS was ruled out by extended dominance as its ICER compared to conservative treatment (£12,071 per QALY gained) was higher than RFA's ICER compared to UGFS (£3,491 per QALY gained).
[d]Results were obtained from Monte Carlo simulation with 10,000 iterations, but authors did not report the credible intervals.
[e]From a societal perspective, CAC, RFA, and HLS were dominated (more costly and less effective) by SVS.
[f]From a health care payer perspective, CAC, EVLA, RFA, and HLS were dominated (more costly and less effective) by SVS.
[g]The probabilities of being cost-effectiveness for other treatments were less than 0.05.

Applicability of the Included Studies

Appendix 5 provides the results of the applicability checklists for the included studies. Both studies were partially applicable to the research question. Given that the costs in European countries were different from those in Canada, their results were not directly applicable to the Ontario setting.

Discussion

Based on current willingness-to-pay values in their respective countries, Epstein et al[13] concluded that RFA was the most cost-effective treatment in the United Kingdom, while Inderhaug et al[95] concluded that EVLA and steam vein sclerosis were the most cost-effective treatments in Norway from both a societal and health care payer perspective. To understand these findings, we briefly discuss the QALYs and costs reported in these two studies.

Both studies showed relatively small differences in QALYs between nonthermal treatments (CAC and MOCA), thermal treatments (RFA, EVLA, and steam vein sclerosis), and surgical vein stripping. Both studies used proxy measures to represent patients' health utility values. Considering the potential uncertainty from the sources of clinical evidence (e.g., treatment success rates) and the utility values and costs of treatments, it is difficult to definitively conclude which treatment is most cost-effective.

Important cost components of treatment for varicose veins, such as costs of overhead and device kits, may vary across settings, so the reported cost-effectiveness results may not be generalizable to Ontario. When evaluating the costs of different treatments, we need to consider that endovenous treatments are conducted at outpatient clinics, while surgical approaches are generally conducted in hospitals. Given no accurate data on overhead costs for the outpatient procedures, the study authors assumed that the overhead costs of endovenous treatments were half those of surgical treatment.[95] Overhead costs can be highly variable across hospitals and countries, and may be related to the size of surgical facilities.[95] Also, the cost of device kits is one of the key cost components of endovenous treatment. The UK economic analysis[13] used the list prices of device kits because the actual prices in purchase agreements are often unknown. This adds further uncertainty to the study results.

Conclusions

Our systematic review of the economic literature identified two studies that evaluated the cost-effectiveness of nonthermal therapies, compared with surgery and thermal therapies, in people with symptomatic varicose veins. Both studies found that thermal ablation procedures were the most cost-effective treatment, although which type of thermal therapy was the optimal strategy depended on the country setting and perspective. None of the studies were conducted from the perspective of the Ontario Ministry of Health. Both studies were partially applicable to the Ontario context.

Primary Economic Evaluation

The published economic evaluations identified in the economic literature review addressed interventions of interest, but none took a Canadian perspective. Owing to these limitations, we conducted a primary economic evaluation.

Research Question

From the perspective of the Ontario Ministry of Health, what is the cost-effectiveness of nonthermal endovenous treatment (mechanochemical ablation [MOCA]) or cyanoacrylate adhesive closure [CAC]) compared with surgical vein stripping or thermal endovenous treatment (endovenous laser ablation [EVLA] and radiofrequency ablation [RFA]) in people with symptomatic varicose veins?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[96]

Type of Analysis

We conducted a cost–utility analysis to determine the costs and health outcomes (i.e., quality-adjusted life-years [QALYs]) associated with each treatment strategy: CAC, MOCA, EVLA, RFA, and surgical vein stripping. We chose this type of analysis because utility inputs are available and QALYs are used as a generic outcome measure, allowing decision-makers to make comparisons across different conditions and treatments.

We conducted a reference case analysis and sensitivity analyses. Our reference case and sensitivity analyses adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[97] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

Target Population

Our target population was adults presenting with symptomatic varicose veins in the saphenous veins of the legs (i.e., large superficial veins). The majority of our target population would be those with great saphenous vein (GSV) insufficiency (with or without small saphenous vein insufficiency). While this description includes anyone of CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification C2 to C6, the model focused on the clinical pathway of patients with C2 to C4 venous disease because this is the population represented in nearly all of the clinical evidence. Patients with advanced venous disease were excluded from the economic model. The definitions of CEAP classification can be found in Table 1 of this report. We limited the population to people with medical need, excluding those seeking treatment for cosmetic purposes. Based on administrative data in Ontario, we estimated that the mean age of our target population is around 55 years and about 63% are females.[98]

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

We conducted evaluations for two nonthermal endovenous treatments (CAC and MOCA) compared with surgical vein stripping (also known as high ligation and stripping) and two thermal endovenous treatments (EVLA and RFA). Among the five treatments included in our analyses, only surgical vein stripping is publicly funded in Ontario, so we considered it as the main comparator. Table 40 summarizes the interventions and comparators evaluated in the economic model.

Table 40: Interventions and Comparators Evaluated in the Primary Economic Model

Interventions	Comparators	Population	Outcomes
Nonthermal endovenous treatments: CAC (e.g., VenaSeal), MOCA (i.e., Clarivein)	Surgical vein stripping (standard of care) Thermal endovenous treatments: EVLA, RFA	Adults with symptomatic varicose veins (CEAP classification C2 to C4) in the saphenous veins of the legs	Costs and QALYs

Abbreviations: CAC, cyanoacrylate adhesive closure; CEAP, Clinical-Etiology-Anatomy-Pathophysiology; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation; QALY, quality-adjusted life-year.

Time Horizon and Discounting

Since only a handful of clinical studies reported clinical outcomes beyond 5 years, our reference case analysis was conducted over a 5-year time horizon. This duration is long enough to cover the recurrence of index symptoms.[13] In accordance with CADTH guidelines,[97] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year.

Main Assumptions

The model's main assumptions for the reference case are:

- **Treatment settings**—Surgical vein stripping would be performed as day surgery in a hospital operating room under general anesthesia, which is the typical practice in Ontario; CAC, MOCA, EVLA, and RFA would be performed at an outpatient clinic with local anesthesia
- **Physician fees**—Physician fees for EVLA and RFA would be the same as those for surgical vein stripping. Since the procedure time for CAC and MOCA is generally shorter than for EVLA and RFA (see Clinical Evidence), we assumed that the physician fees for CAC and MOCA were 80% of those for surgical vein stripping
- **Omitted costs**—We omitted costs that are roughly equal across different procedures, such as preoperative assessment and postoperative follow-up (i.e., the 1-week check for complications and the 8-week assessment for vein closure)
- **Retreatment**—After the first treatment, people with symptomatic varicose veins may receive a second treatment on the GSV due to failure of the index treatment or symptom recurrence. We assumed the success rate for retreatment would be 100% (we removed this assumption in a scenario analysis)

- **Complications**—We did not model major complications, such as deep vein thrombosis, because they are rare for all treatments (see Clinical Evidence). Minor complications, such as pain after treatment, were captured by the utility loss during the postprocedural recovery period

Model Structure

When developing the economic model, we reviewed a number of earlier models from Canada and the United Kingdom for treatments of symptomatic varicose veins.[13,99,100] We included five treatments: surgical vein stripping, EVLA, RFA, CAC, and MOCA. We developed a Markov model to evaluate the cost-effectiveness of these treatments. The length of the Markov cycle is one month. As illustrated in Figure 11, the Markov model included five health and treatment states after the index intervention:

- **Recovery after the index treatment**—People with symptomatic varicose veins experienced a short recovery period after their initial treatment: 2 weeks for surgical vein stripping and 1 week for nonthermal and thermal endovenous treatments.[13] This period covers the occurrence of short-term complications including localized pain
- **Adjunct sclerotherapy for residual varicosities**—Physicians may not treat all varicosities in a single procedure. Six weeks after the index treatment, a small proportion of people with symptomatic varicose veins may receive ambulatory sclerotherapy for residual varicosities. This procedure is considered an adjunct therapy, not a failure of the index treatment or a retreatment
- **Success**—This refers to post-treatment clinical success (improved symptoms, functioning, and health-related quality of life) after the index treatment and recovery period or adjunct sclerotherapy. People in the "Success" health state do not require retreatment or further adjunct treatment. Although a small proportion of people in this health state may not have complete occlusion of the treated great saphenous vein (i.e., the treatment may not have achieved technical or anatomical success), they have improved symptoms and do not need further treatment. These people are still considered to have achieved treatment success
- **Retreatment of the great saphenous vein**—After 6 months following the index treatment, people with symptomatic varicose veins may experience retreatment of the GSV due to either a failure of the initial treatment or a recurrence of varicosity
- **Death**—In all health states, people with symptomatic varicose veins have the same risk of death as the general population (i.e., age- and sex-specific death rates for Ontario, Canada)

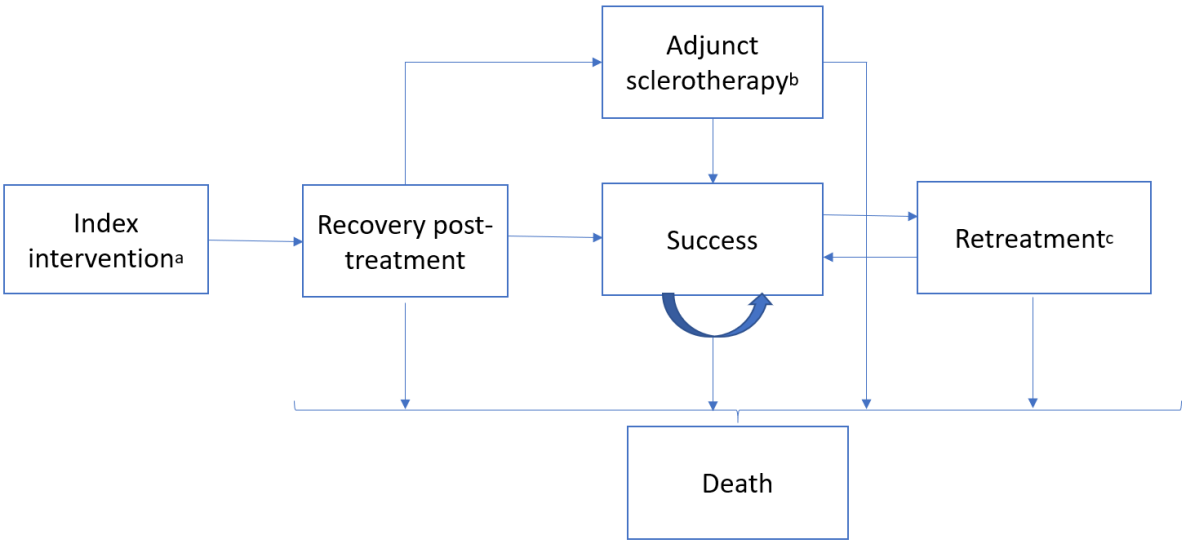

Figure 11: Model Structure, Economic Evaluation of Endovenous Treatments for Varicose Veins

[a]We included 5 treatment strategies: surgical vein stripping, endovenous laser ablation, radiofrequency ablation, cyanoacrylate adhesive closure, and mechanochemical ablation.
[b]A proportion of people with symptomatic varicose veins may receive ambulatory sclerotherapy (an adjunct therapy) for residual varicosities.
[c]People with symptomatic varicose veins may experience retreatment on the great saphenous vein due to the failure of the initial treatment or recurrence.

Clinical Outcomes and Utility Parameters

We used several input parameters to populate the model, such as:

- Rates of retreatment (specific to each treatment) from 6 months to 5 years
- Proportion of people with symptomatic varicose veins receiving post-treatment sclerotherapy for residual varicosities (i.e., adjunct sclerotherapy)
- Health state utilities (i.e., health-related quality of life)

CLINICAL PARAMETERS

Table 41 presents the model's clinical parameters, and we describe them briefly here.

Retreatment of the Great Saphenous Vein

The key clinical parameter was the rate of retreatment. Either a failure after the initial treatment or a recurrence that leads to renewed symptoms or adversely impacts quality of life would result in retreatment. As noted, not all people with incomplete occlusion of the treated great saphenous vein need retreatment. For many patients, clinical symptoms and quality of life are improved after treatment despite incomplete vein closure.

Retreatment may happen after 6 months from the initial treatment at a roughly constant rate for the five treatments.[13] The cost–utility analysis from the United Kingdom estimated that, after surgical treatment, the rate of retreatment of the great saphenous vein was 3.4 per 100 patient-years.[13] Based on the odds ratios for retreatment determined in the UK meta-analysis,[13] we calculated retreatment rates for RFA (1.92 per 100 patient-years) and for EVLA (3.28 per 100 patient-years). The footnote to Table 41 provides details of the calculation process.

In our clinical evidence review, there were insufficient data to compare retreatment between procedures. Many studies did not report retreatment, and successful vein closure was the primary outcomes in most studies. Therefore, to estimate retreatment rates for CAC and MOCA, we assumed that the odds ratios for retreatment were the same as the odds ratios for procedure failure and recanalization (for CAC versus EVLA and MOCA versus RFA). Based on the odds ratio for CAC versus EVLA (0.51, 95% CI 0.22–1.23), we calculated a retreatment rate of 1.86 per 100 patient-years for CAC (see Table 41). However, when using the odds ratio for MOCA versus RFA (mean 3.65, 95% CI 1.34–9.93) and the retreatment rate for RFA (1.92 per 100 patient-years), we found that the estimated retreatment rate for MOCA was higher than for surgical vein stripping. This estimate was inconsistent with what we've seen broadly in the literature or heard from clinicians because the risk of neovascularization and reintervention after surgery is generally higher than after endovenous therapy. Although no direct comparison studies are available, Epstein et al, 2018[13] reported that the odds ratio of GSV retreatment for MOCA versus surgery was 0.46 (95% CI 0.01–29.92), favouring MOCA in point estimate but having very wide 95% confidence intervals. Given the inconsistent evidence from different sources, we assumed that MOCA and surgery had equivalent retreatment rates in the economic model.

There is large uncertainty as to which procedure is typically used for retreatment. We assumed that the index treatment does not impact the selection of retreatment modality. Following earlier cost–utility studies from the United Kingdom,[13,100] we estimated that, among all patients needing retreatment, these subsequent procedures would be proportioned as follows: sclerotherapy (day surgery), 42%; EVLA, 46%; and surgical vein stripping, 12%.

Adjunct Sclerotherapy for Residual Varicosities

After the index treatment, a proportion of people with symptomatic varicose veins will also receive sclerotherapy or phlebectomy for residual varicosities. There are two schools of thought about this adjunct treatment in people undergoing treatment of a truncal vein (i.e., the great saphenous vein or small saphenous vein).[101] The first suggests simultaneously treating the truncal vein and other varicosities (concomitant procedures), which increases the time of treatment. The second approach suggests delaying adjunct treatment until after the main procedure, to first assess the outcome of truncal vein treatment and then determine the need for further treatment. Due to these and other considerations in the index treatment, the proportion of people receiving adjunct therapy varied greatly across clinical studies[13,99] and often depends on the clinical protocol used in a particular centre. In the economic evaluation, we aimed to quantify the difference in costs and QALYs driven by the index treatments, so we assumed that other factors such as variations in adjunct therapy were similar between groups. In the reference case, we assumed that most people would receive concomitant procedures (when adjunct treatment was necessary), and we estimated that 2% of people would receive ambulatory sclerotherapy at 6 weeks after the index treatments for all five treatment groups.[101] In scenario analyses, we varied the proportions of adjunct sclerotherapy for different treatments.

Mortality

Generally, symptomatic varicose veins are not considered life-threatening, but this condition can impact the quality of life.[13] For simplicity, we assumed that people with symptomatic varicose veins in any health state would have the same age- and sex-specific mortality rate as the general population in Ontario.[102]

Table 41: Clinical Inputs Used in the Economic Model to Evaluate Treatments for Varicose Veins

Model Parameter	Mean (95% CI)	Distribution (Parameters)	Reference
Rate of Retreatment on GSV, 6 Months Post-Procedure, per 100 Person-Years			
Surgical vein stripping	3.4 (2.1, 5.5)	Lognormal (Mean: −3.383; SE: 0.245)	Epstein et al, 2018[13]
Odds Ratio of Retreatment on GSV[a]			
RFA versus surgical vein stripping	0.51 (0.24, 1.08)	Lognormal (Mean: −0.673; SE: 0.384)	Epstein et al, 2018[13]
RFA versus EVLA	0.62 (0.31, 1.25)	Lognormal (Mean: −0.478; SE: 0.356)	Epstein et al, 2018[13]
CAC versus EVLA	0.51 (0.22, 1.23)	Lognormal (Mean: −0.673; SE: 0.439)	Clinical Evidence Review
MOCA versus surgical vein stripping	1	Uniform (0.75, 1.25)	Assumption
Retreatment Procedure as Proportion of All Patients Receiving Retreatment			
Sclerotherapy (day surgery)	42% (33%, 52%)	Dirichlet (42, 12, 46)	Epstein et al, 2018; Tassie et al, 2014[13,100]
Surgical vein stripping	12% (6%, 19%)		
EVLA	46% (36%, 55%)		
Proportion of Patients Receiving Adjunct Sclerotherapy for Residual Varicosities After Index Treatment			
Surgical vein stripping	1.96% (0.05%, 10.45%)	Beta (1, 50)	Lane et al, 2015[101]
EVLA	1.96% (0.05%, 10.45%)	Beta (1, 50)	Lane et al, 2015[101]
RFA	1.96% (0.05%, 10.45%)	Beta (1, 50)	Lane et al, 2015[101]
CAC	1.96% (0.05%, 10.45%)	Beta (1, 50)	Lane et al, 2015[101]
MOCA	1.96% (0.05%, 10.45%)	Beta (1, 50)	Lane et al, 2015[101]

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; EVLA, endovenous laser ablation; GSV, great saphenous vein; MOCA, mechanochemical ablation; RFA, radiofrequency ablation; SE, standard error.

[a]The process of estimating retreatment rates in the probabilistic analyses was as follows, using RFA as the example: We generated lognormal distribution data for the retreatment rate for surgical vein stripping (after log transformation: mean of −3.383, SE of 0.245). We translated this rate into a probability, and then translated the probability into odds of retreatment. The meta-analysis showed that the odds ratios of retreatment after RFA versus surgery was 0.51 (95% CI 0.24–1.08).[13] The odds ratio was assigned the lognormal distribution (after log transformation: mean of −0.673, SE of 0.384). Based on the odds of retreatment after surgical vein stripping and the odds ratio of retreatment after the RFA versus surgical treatment, we calculated the odds of retreatment after RFA. Then, we translated the odds into the probability of retreatment, and finally we translated this probability into a rate of retreatment. From 10,000 simulations, we calculated the retreatment rate after RFA to be 1.92 (SE 0.86) per 100 patient-years. Using the same approach, we calculated retreatment rates for EVLA, CAC, and MOCA.

HEALTH STATE UTILITIES

Table 42 presents the health state utilities used in the economic model. We did not identify published health state utilities that exactly fit the health states defined in our Markov model. For example, some clinical trials reported health state utilities at baseline and at different follow-up times. The utilities were associated with each treatment for symptomatic varicose veins,[101] but not associated with specific health states (e.g., full success, retreatment). Published economic modelling studies applied a proxy measure for the utilities;[13,99] since there were no measures for the health state utilities, authors approximated the utilities using values for before versus after treatment in people with symptomatic varicose veins in clinical trials.[101] Therefore, based on a cost–utility study from the United Kingdom in 2018,[13] we used the proxy utility values described in Table 4. The parameters for Beta distribution and Gamma distribution were calculated based on the mean and standard error (SE).[103]

Table 42: Utilities Used in the Economic Model to Evaluate Treatments for Varicose Veins

Health State or Treatment State	Utility or Disutility, Mean (SE)	Distribution	Duration	Reference
Clinical success	0.846 (0.085)[a]	Beta	Entire duration	Epstein et al, 2018[13]
Recovery post procedure				
Surgical vein stripping	−0.05 (0.01)[a]	Gamma[b]	2 wk post-surgery	Epstein et al, 2018[13]
EVLA, RFA, CAC, MOCA	−0.05 (0.01)[a]	Gamma[b]	1 wk post-surgery	Epstein et al, 2018[13]
Sclerotherapy for residual varicosities	−0.127 (0.054)	Gamma[b]	6 wk before adjunct treatment	Epstein et al, 2018[13]
Retreatment	−0.127 (0.054)	Gamma[b]	6 mo before retreatment	Epstein et al, 2018[13]

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; mo, month(s); MOCA, mechanochemical ablation; RFA, radiofrequency ablation; SE, standard error; wk, week(s).

[a]We assumed that the SE was 10% of the mean for utility of full success and 20% of the mean for disutility values since the SE was not reported.

[b]The absolute values of disutility (noted by the negative values in second column) follow Gamma distributions.

Cost Parameters

Costs were expressed in 2020 Canadian dollars.[104] We present the costs of five treatments for varicose veins in Table 43. Currently, only surgical vein stripping is publicly funded in Ontario, and EVLA, RFA, CAC, and MOCA are available as noninsured services in private clinics, though a minority of people with symptomatic varicose veins may have some coverage through private health insurance. We used the Ontario Case Costing Initiative tool to determine the hospital cost of surgical vein stripping (patient type: day surgery), including the costs of operating room, post-anesthetic recovery room, pre- and postoperative care, laboratory, pharmacy, and overhead.[105] Total procedure costs were calculated by summing the hospital cost and professional fees.

Given that EVLA, RFA, CAC, and MOCA are not currently available in Ontario's public health care system, and there are considerable variations in clinical practice across private clinics (e.g., professionals involved, treatment rooms required), it is difficult to accurately estimate the cost of these treatments. Furthermore, the price of device kits, disposables, and equipment may also vary across health centres based on purchase agreements between clinics and suppliers (e.g., lower prices with larger quantities

purchased).[13,106] Thus, we roughly estimated the procedure costs by considering several cost components:

- **Outpatient nursing—**An earlier report from the Institute of Health Economics (Edmonton, Alberta) estimated that EVLA and RFA procedures are performed by 2 nurses for approximately 3 hours.[99] These procedures include preparation, procedure care, and postprocedural care. We assume that nursing hours required for EVLA and RFA are same as for CAC and MOCA. The median salary of a registered nurse in Ontario is approximately $36 per hour,[107] and the cost of employee benefits, such as employment insurance, pension plans, and extended health coverage, are estimated to be approximately 33% of salaries.[108] We thus estimated the cost of nursing to be $48 per hour, or $287 for 6 hours of work per procedure
- **Professional fees—**We assumed that physician fees and surgical assistance fees for EVLA and RFA are equivalent to those for surgical vein stripping. As the procedure time for CAC and MOCA is shorter than that for EVLA and RFA,[66,76] we assumed that physician fees and surgical assistance fees for CAC and MOCA are 80% of those for surgical vein stripping
- **Equipment and maintenance:**
    - The endovenous procedures are generally guided by ultrasound. We estimated the cost of ultrasound equipment (including 2-year warranty) was $40,000 and the maintenance service was $3,000 per year after 2 years (written communication, Salient Medical Solutions, April 2020). Thus, the total 5-year cost for using ultrasound is $49,000. We also assumed that, on average, one clinic would offer 500 endovenous procedures over 5 years (i.e., 100 procedure per year) and that the service life of equipment was 5 years. Then, the cost of ultrasound per procedure would be about $98 ($49,000 ÷ 500) over 5 years
    - The cost of a laser generator (used for EVLA) is $35,000 and the cost for maintenance after 1 year is $3,000, so the 5-year total costs for this equipment would be $47,000 (written communication, Salient Medical Solutions, April 2020). Then, the per-procedure cost of a laser generator would be about $94 ($47,000 ÷ 500). The total equipment cost (including maintenance) per EVLA procedure would therefore be $192 ($98 + $94).
    - We did not find reliable cost data for the radiofrequency energy generator (used in RFA) or the ClariVein system (for MOCA), so we therefore assumed the equipment costs for RFA and MOCA were the same as for EVLA, $192 per procedure. CAC treatment does not need a major capital investment for the treatment system, so its equipment cost was $98 per procedure for ultrasound
- **Device kit**—We obtained the cost of an EVLA device kit, $350 per procedure (including laser fiber and micro access kit), from a manufacturer (written communication, Salient Medical Solutions, April 2020). According to a private clinic in Ontario, the cost of a CAC device kit is around $1,200 per procedure (telephone communication, Dr. David Szalay, June 2020). Based on published economic studies, we estimated that the cost of device kits for RFA and MOCA would be $769[106] and $815,[13] respectively (after adjusting for inflation using Statistics Canada's Consumer Price Index[104])
- **Disposable materials—**In general, the endovenous procedures we evaluated have similar costs for disposable materials, around $370 per procedure. We obtained these costs from a private clinic in Ontario (written communication, Vascular Health Bronte, May 2020). The costs included

endovenous custom pack, procedure pack, sterile tubing, micro-puncture kit, access sheath, local anesthetic, sterile gloves, sterile gowns, and so on

- **Overhead—**EVLA, RFA, CAC, and MOCA procedures are conducted in outpatient clinics. Based on data from the Ontario Case Costing Initiative for the case mix group c212 – varicose vein strip/ligation, overhead costs in an ambulatory care setting are much less then those in a day surgery setting (which generally requires an operating room).[105] Clinics that perform RFA or EVLA are required to have routinely scheduled inspections from the College of Physicians and Surgeons of Ontario.[109] Clinics that perform only CAC or MOCA do not have these inspection requirements. Therefore, we expected that the overhead costs for RFA and EVLA would be greater than those for CAC and MOCA. We estimated that the overhead costs for RFA and EVLA would be about 75% of the overhead costs for surgical vein stripping conducted in an operating room, and that the overhead costs of CAC and MOCA would be half of those for surgical vein stripping

Table 43: Costs Used in the Economic Model to Evaluate Treatments for Varicose Veins

Variable	Cost per Procedure, $[a]					Source
	Surgical Vein Stripping	EVLA	RFA	CAC	MOCA	
Hospital cost (day surgery in OR)	1,727 (SE: 18)	NA	NA	NA	NA	OCCI data[105,b]
Outpatient nursing	NA	287	287	287	287	IHE report; Government of Canada[99,107]
Professional fees						Schedule of Benefits[36]
Surgeon	400 (R837: 200 + R868: 200)[c]	400	400	320	320	
Surgical assistant	120 (6 basic units + 4 time units)	120	120	96	96	
Anesthetist	165 (7 basic units + 4 time units)	NA	NA	NA	NA	
Equipment and maintenance (e.g., ultrasound, laser)	NA	192	192[c]	98[c]	192[c]	Salient Medical Solutions[d]
Device kit	NA	350	769	1,200	815	Salient Medical Solutions[d]; expert consultation[e]; Epstein et al, 2018[2]; Butt and Kopriva, 2018[13,106]
Disposable materials	NA	370	370	370	370	Vascular Health Bronte[f]
Overhead	805 (SE: 12)	604	604	403	403	OCCI data[105,b]
Total direct cost (excluding overhead)	2,412	1,720	2,139	2,372	2081	
Total costs (including overhead)	**3,217[g]**	**2,324[g]**	**2,743[g]**	**2,774[g]**	**2,483[g]**	

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; IHE, Institute of Health Economics; MOCA, mechanochemical ablation; NA, not applicable; OCCI, Ontario Case Costing Initiative; OR, operating room; RFA, radiofrequency ablation; SE, standard error.

[a]In 2020 Canadian dollars.

[b]In the OCCI portal, we searched the costs for the principal procedure of surgical vein stripping in legs (Canadian Classification of Health Interventions [CCI] code: 1KR87WM, open approach with stripping technique).[105] Hospital costs are costs directly related to providing patient care and include nursing, operating room, pharmacy, and labs. Overhead costs (i.e., indirect costs) include administration, finance, human resources, plant operations, etc. and were obtained from OCCI data reported in 2017/18.

[c]Typically, R868 (high ligation and stripping of long saphenous vein with groin dissection) and R837 (multiple ligation and avulsion) are billed together during standard GSV stripping plus below-knee varicose avulsions.[36]

[d]Written communication, Salient Medical Solutions, April 2020.

[e]Telephone communication, Dr. David Szalay, June 2020.

[f]Written communication, Vascular Health Bronte, May 2020.

[g]Numbers may be inexact due to rounding.

Table 44 presents the cost of sclerotherapy as adjunct therapy for residual varicosities and retreatment of the GSV due to failure of index treatment or symptom recurrence.

Table 44: Costs of Sclerotherapy for Adjunct Therapy and Retreatment

Variable	Adjunct Therapy of Residual Varicosities, Ambulatory Care, $[a]	Retreatment of GSV, Day Surgery, $[a]	Source
Hospital cost	200	277	OCCI[105]
Overhead	44	70	OCCI[105]
Professional fees	77.85	77.85	Schedule of Benefits[36]
Total costs	**322**	**425**	

Abbreviations: GSV, great saphenous vein; OCCI, Ontario Case Costing Initiative.
[a]In 2020 Canadian dollars.

We assumed that the costs of retreatment using surgical vein stripping and EVLA are same as those for the initial treatment. We calculated that the weighted cost for retreatment was $1,633 per procedure, based on the proportions of retreatments that would be done via sclerotherapy (42%), EVLA (46%), and surgical vein stripping (12%) (see Table 41).

We assigned Gamma distributions for the cost data in the probabilistic analyses. The parameters for Gamma distribution were calculated based on the mean and SE.[103] For cost data with only a point estimate, we assumed that the SE was 20% of the mean in the probabilistic analyses.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) to simultaneously capture the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. We calculated the mean costs with 95% credible interval (CrI, i.e., 2.5th and 97.5th percentiles from the Monte Carlo simulations) and mean QALYs with 95% CrI for each treatment assessed.

Following the CADTH guidelines,[97] we reported the sequential incremental cost-effectiveness ratios (ICER) and an ICER produced from a common comparator (i.e., surgical vein stripping). We ordered the treatments by the average total costs, from the lowest to the highest. For sequential ICERs, after excluding treatments that were either dominated or subject to extended dominance, we calculated the ICER for a less costly comparator compared with the next more costly comparator. In addition to estimating the ICER for each comparison, we also used net monetary benefit (NMB) to evaluate the cost-effectiveness of the five included treatments (see Glossary, *Incremental net benefit*). We considered commonly used willingness-to-pay (WTP) values of $50,000 to $100,000 per QALY in this study.

The results of the probabilistic analysis are also presented on a cost-effectiveness acceptability curve. We present uncertainty quantitatively as the probability that a treatment is cost-effective at WTP values from $0 to $200,000 per QALY. For each simulation, the treatment with the maximum NMB at the given WTP was considered as the most cost-effective among the five treatments we compared.[110] The probability of being cost-effective for each treatment was equal to the proportion of the 5,000 simulations for which this treatment had the highest NMB.

SCENARIO ANALYSES

We also conducted the following scenario analyses to examine the cost-effectiveness of treatments for varicose veins:

- Scenario 1: applying different time horizons, 1 year (Scenario 1-1) and 10 years (Scenario 1-2)
- Scenario 2: assuming that the retreatment rates for all treatments are two times higher than in the reference case
- Scenario 3: accounting only for direct health care costs, omitting overhead costs
- Scenario 4: excluding the costs of equipment and maintenance for EVLA, RFA, CAC, and MOCA (e.g., assuming that these costs would be covered by negotiation with suppliers as part of the purchase of device kits)
- Scenario 5: assuming higher likelihood of patients receiving adjunct sclerotherapy after EVLA, RFA, CAC, and MOCA (i.e., to follow the second school of thought regarding this additional therapy). In this scenario, the probability of receiving adjunct sclerotherapy after any of the four endovenous treatments was 0.36 (Beta distribution [alpha: 18; beta: 32]);[101] for surgical vein stripping, the chance of receiving adjunct sclerotherapy was same as in the reference case
- Scenario 6: assuming lower and higher costs of disposable materials and device kits for EVLA, RFA, CAC, and MOCA (Scenario 6-1: 75% of the reference case; Scenario 6-2: 125% of the reference case). In Scenario 6-3, since CAC is the main intervention of interest and its cost may be discounted given a potential large volume, we assumed that the cost of a CAC device kit was $720 per procedure (vs. $1,200 in the reference case) and kept the costs of other device kits the same as the reference case
- Scenario 7: considering failures of retreatment, instead of assuming a 100% success rate in the retreatment on the GSV. In this scenario, patients who fail retreatment would receive a third treatment. For surgical vein stripping and EVLA, retreatment failure rates were the same as in the index treatments. Based on Epstein et al, 2018,[13] we estimated the odds ratio of failure for sclerotherapy versus surgical vein stripping was 5.48 (95% CI: 2.57–11.70), and the calculated failure rate was 16.9 per 100 patient-years
- Scenario 8: assuming that no retreatments on the GSV occurred over the 5-year time horizon. In this scenario, patients whose index treatment failed would stay in a state of lower health-related quality of life (disutility: 0.127[13]) for the remaining time
- Scenario 9: assuming that the disutility of retreatment was two times higher than in the reference case
- Scenario 10: estimating the retreatment rate after CAC using results from Ay et al, 2020[92] (Scenario 10-1) and Bozkurt and Yilmaz, 2016[48] (Scenario 10-2), instead of using results from our meta-analysis, as in the reference case. In Ay et al[92] the odds ratio for retreatment after CAC

versus RFA was 1.45 (95%CI: 0.59 to 3.55), favouring RFA, and the odds ratio for CAC versus EVLA was 0.52 (95%CI: 0.19 to 1.45) also favoring CAC in Bozkurt and Yilmaz[48]

Results

Reference Case Analysis

Table 45 presents the reference case results, from lowest to highest total costs. In this analysis, we first compared each endovenous treatment with surgical vein stripping. Surgical vein stripping had the highest expected cost and the lowest expected QALYs among the five treatments, so it was dominated by the other four treatments.

We further conducted analyses of sequential ICERs. The four endovenous treatments had similar QALYs over 5 years. MOCA was dominated by EVLA (i.e., MOCA was more costly and less effective than EVLA). RFA was ruled out by extended dominance, as the ICER of RFA compared with EVLA ($110,500) was higher than the ICER of CAC compared with EVLA ($108,425). After ruling out treatments by dominance or extended dominance, only EVLA and CAC were left. The ICER of CAC versus EVLA ($108,425/QALY) exceeds a WTP of $100,000 per QALY. When we assumed WTP values of $50,000 and $100,000 per QALY, EVLA was associated with the highest NMB among the five treatments. Based on ICERs and NMB, EVLA was likely to be the most cost-effective strategy among the five treatments for the management of symptomatic varicose veins.

Given that the difference in QALYs among the five treatments was small, the cost-effectiveness results (e.g., ruling out RFA due to extended dominance) were associated with considerable uncertainty. We further address this uncertainty when we present the cost-effectiveness acceptability curve and scenario analyses (e.g., Scenario 10), below.

Table 45: Results of Cost–Utility Analysis of Treatments for Varicose Veins, Reference Case

Strategy	Average Total Costs (95% CrI), $	Average Total Effects (95% CrI), QALY	ICER, $/QALY	
			Vs. Surgical Vein Stripping	Sequential ICER[a]
EVLA	2,528.81 (2,182.23; 2,947.58)	4.0571 (3.0934; 4.6544)	Dominant[b]	—
MOCA	2,711.86 (2,319.19; 3,161.61)	4.0565 (3.0948; 4.6540)	Dominant[b]	Dominated[c]
RFA	2,872.18 (2,473.50; 3,316.40)	4.0602 (3.0967; 4.6586)	Dominant[b]	Extended dominance[d]
CAC	2,894.47 (2,378.67; 3,504.89)	4.0605 (3.0970; 4.6593)	Dominant[b]	108,425
Surgical vein stripping	3,444.3 (3,237.28; 3,688.95)	4.0555 (3.0925; 4.6538)	—	Dominated[e]

Abbreviations: CAC, cyanoacrylate adhesive closure; CrI, credible interval; EVLA, endovenous laser ablation; ICER, incremental cost-effectiveness ratio; MOCA, mechanochemical ablation; QALY, quality-adjusted life-year; RFA, radiofrequency ablation.
[a]Some numbers may appear inexact due to rounding.
[b]The endovenous treatment is less costly and more effective than surgical vein stripping.
[c]MOCA was more costly and less effective than EVLA.
[d]RFA was ruled out by extended dominance, as the ICER of RFA vs. EVLA ($110,500 /QALY) was higher than for CAC vs. EVLA ($108,425/QALY).
[e]Surgical vein stripping was more costly and less effective than CAC.

Cost-Effectiveness Acceptability Curve

Figure 12 presents results of the probabilistic analyses as a cost-effectiveness acceptability curve. When the willingness-to-pay values were less than $100,000 per QALY, EVLA had the highest probabilities of being cost-effectiveness among the five treatments. Moreover, surgical vein stripping had very little to no chance of being cost-effective at any WTP. For CAC, however, the probability of being cost-effective increased with increasing WTP values. When the WTP was more than $125,000 per QALY, CAC had the highest probability of cost-effectiveness among the five treatments.

When the WTP was $50,000 per QALY gained, the probabilities of being cost-effective were 55.6%, 15.6%, 10.0%, 18.8%, and 0%, for EVLA, MOCA, RFA, CAC, and surgical vein stripping, respectively. When the WTP was $100,000 per QALY gained, the probabilities of being cost-effective were 40.2%, 12.1%, 17.7%, 30.0%, and 0%, for EVLA, MOCA, RFA, CAC, and surgical vein stripping, respectively.

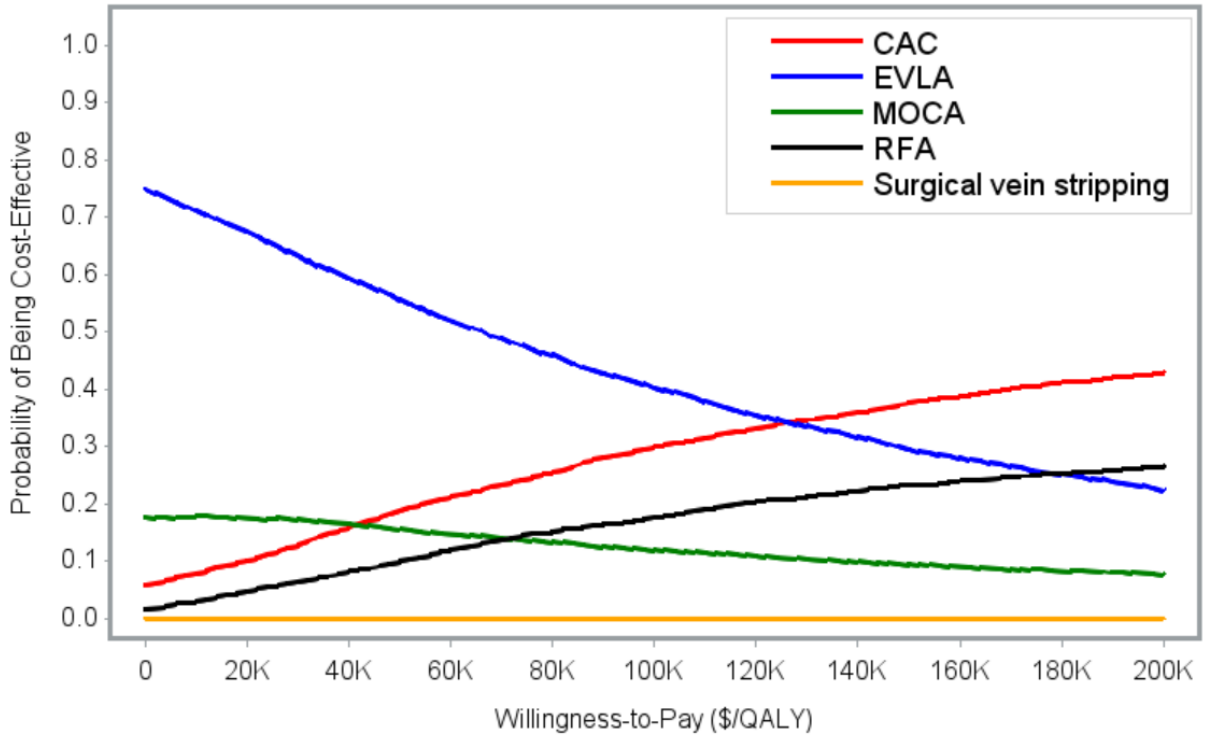

Figure 12: Cost-Effectiveness Acceptability Curve: Treatments for Varicose Veins

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; QALY, quality-adjusted life-year; RFA, radiofrequency ablation.

In Figure 13, we present a cost-effectiveness plane showing the incremental costs and incremental QALYs of CAC versus EVLA. The results were consistent with the reference case analysis (e.g., a small proportion of simulations were below the WTP value of $50,000 per QALY gained).

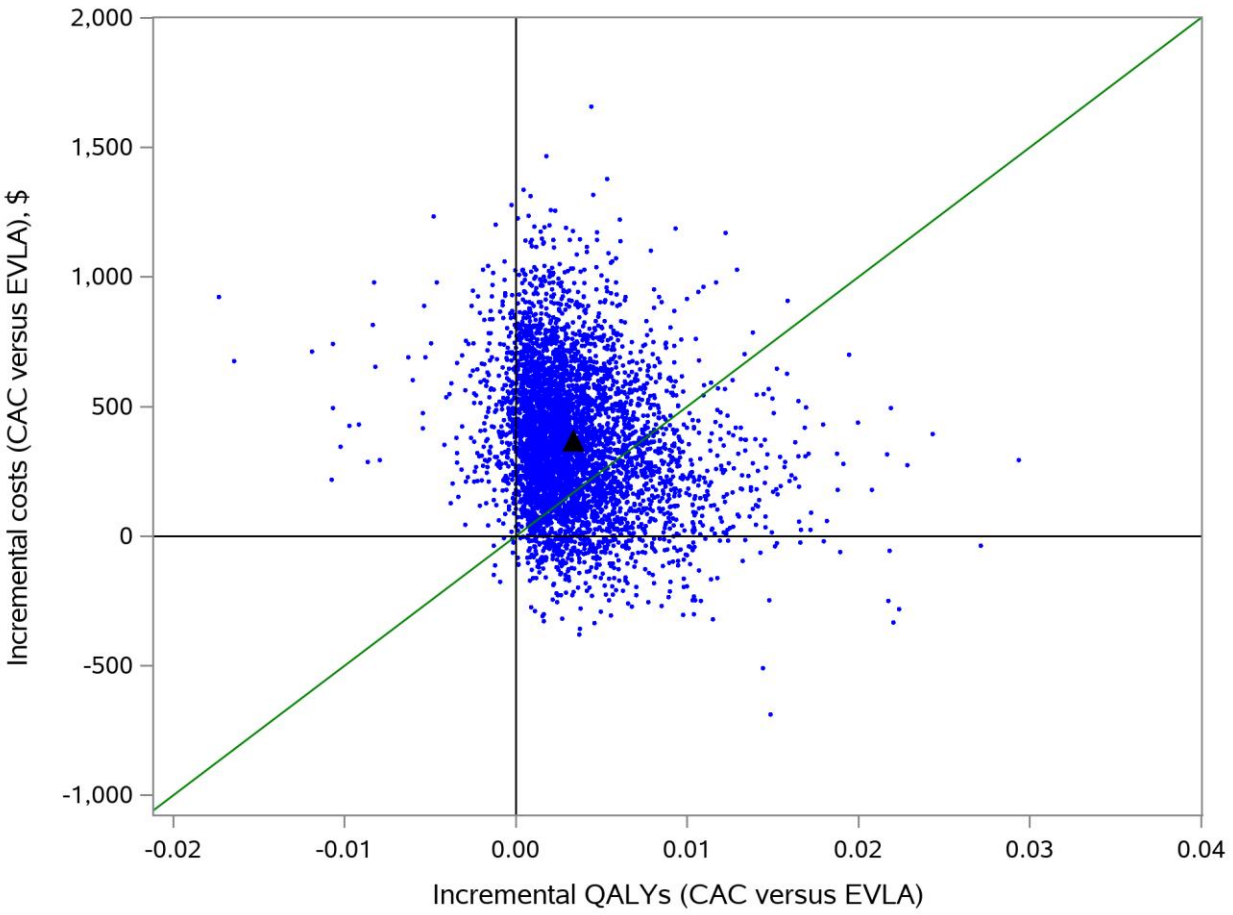

Figure 13: Cost-Effectiveness Plane: Incremental Costs and Incremental QALYs of Cyanoacrylate Adhesive Closure vs. Endovenous Laser Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; QALY, quality-adjusted life-year.
The black triangle in the centre of the dots indicates the reference case scenario. Each blue dot surrounding the black triangle represents a single result from the simulation, presenting the incremental effects and incremental costs of CAC versus EVLA. The green diagonal line represents a willingness-to-pay value of $50,000 per QALY gained.

Scenario Analyses

Table 46 presents the results of the scenario analyses, excluding the dominated strategies and those ruled out by extended dominance. The scenario analyses were consistent with the reference case. In most scenarios, MOCA and surgical vein stripping were dominated, and RFA was unlikely to be cost-effective compared with EVLA (ICER > $100,000 per QALY gained or RFA was an extended dominance strategy). RFA and CAC had very similar QALYs in most scenarios. In Scenario 10-1 (where we assumed CAC was associated with a higher retreatment rate than RFA), RFA dominated CAC.

EVLA was the most cost-effective treatment in most scenarios, while CAC became more cost-effective than EVLA (i.e., ICERs of CAC versus EVLA were around $50,000 or less than $50,000 per QALY gained) in the following scenarios:

- Time horizon of 10 years (ICER of $50,363 in Scenario 1-2)

- Higher retreatment rates (ICER of $50,304 in Scenario 2)
- Lower costs of disposable materials and device kits (ICER of $46,750 in Scenario 6-1; dominant in Scenario 6-3)
- No retreatment on the great saphenous vein (ICER of $28,896 in Scenario 8)
- Higher disutility of retreatment (ICER of $54,212 of Scenario 9)

The costs of device kits for the four endovenous treatments substantially impacted the cost-effectiveness results (Scenario 6), while real-world prices for the device kits via negotiated purchase agreements) are difficult to accurately estimate. Also, using different sources for clinical and/or cost parameters (as we did in Scenario 10) may produce different results. Therefore, it is difficult to make definitive conclusions as to which treatment is most cost-effective among the five options modelled.

Table 46: Results of Cost–Utility Analysis of Treatments for Varicose Veins, Scenario Analyses

Strategy, Excluding Dominated	Average Total Costs, $	Sequential Incremental Cost[a], $	Average Total Effects, QALY	Sequential Incremental Effect[b], QALY	Sequential ICER[c], $/QALY
Reference Case					
EVLA	2,528.81		4.0571		
CAC	2,894.47	365.65	4.0605	0.0034	108,425
Scenario 1-1: 1-Year Time Horizon					
EVLA	2,345.48		0.8424		
RFA	2,759.24	413.76	0.8428	0.0004	1,172,657
CAC	2,787.48	28.23	0.84282	0.00002	1,301,781
Scenario 1-2: 10-Year Time Horizon					
EVLA	2,702.21		7.7234		
CAC	3,002.11	299.90	7.7294	0.0060	50,363
Scenario 2: Retreatment Rates 2 X Higher Than in Reference Case					
EVLA	2,705.26		4.0502		
CAC	3,005.06	299.79	4.0562	0.0060	50,304
Scenario 3: Include Direct Health Care Costs Only					
EVLA	1,877.69		4.0571		
RFA	2,239.29	361.60	4.0602	0.0031	116,369
CAC	2,464.38	225.09	4.0605	0.0003	849,274
Scenario 4: Exclude Equipment and Maintenance Costs (for EVLA, RFA, CAC, and MOCA)					
EVLA	2,326.46		4.0571		
RFA	2,673.51	347.05	4.0602	0.0031	111,685
CAC	2,789.80	116.28	4.0605	0.0003	438,733

Strategy, Excluding Dominated	Average Total Costs, $	Sequential Incremental Cost[a], $	Average Total Effects, QALY	Sequential Incremental Effect[b], QALY	Sequential ICER[c], $/QALY
Scenario 5: Higher Likelihood of Adjunct Sclerotherapy (for EVLA, RFA, CAC, and MOCA)					
EVLA	2,638.48		4.0521		
CAC	3,004.14	365.65	4.0555	0.0034	108,425
Scenario 6-1: Lower Costs of Disposable Materials and Device Kits (for EVLA, RFA, CAC, and MOCA)					
EVLA	2,338.88		4.0571		
CAC	2,496.55	157.66	4.0605	0.0034	46,750
Scenario 6-2: Higher Costs of Disposable Materials and Device Kits (for EVLA, RFA, CAC, and MOCA)					
EVLA	2,718.74		4.0571		
RFA	3,163.62	444.89	4.0602	0.0031	143,170
CAC	3,292.39	128.76	4.0605	0.0003	485,819
Scenario 6-3: Lower Cost of Device Kit for CAC, $720 per Procedure					
CAC	2,415.52		4.0605		Dominant
Scenario 7: Include Retreatment Failures and Allow a Third Treatment on the GSV					
EVLA	2,562.07		4.0558		
CAC	2,913.62	351.55	4.0598	0.0039	89,485
Scenario 8: No Retreatment on the GSV					
EVLA	2,323.51		4.0285		
CAC	2,775.05	451.53	4.0441	0.0156	28,896
Scenario 9: Disutility of Retreatment 2X Higher Than in Reference Case					
EVLA	2,528.81		4.0491		
CAC	2,894.47	365.65	4.0558	0.0067	54,212
Scenario 10-1: Estimate Retreatment Rate for CAC Based on Ay et al, 2020[92]					
EVLA	2,528.81		4.0571		
RFA	2,872.18	343.37	4.0602	0.0031	110,500
Scenario 10-2: Estimate Retreatment Rate for CAC Based on Bozkurt and Yilmaz, 2016[48]					
EVLA	2,528.81		4.0571		
RFA	2,872.18	343.37	4.06024	0.0031	110,500
CAC	2,900.19	28.01	4.06028	0.00004	628,786

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; GSV, great saphenous vein; ICER, incremental cost-effectiveness ratio; RFA, radiofrequency ablation.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Incremental effect = average effect (strategy B) − average effect (strategy A).

[c]Some numbers may appear inexact due to rounding.

Discussion

Our economic evaluation showed that surgical vein stripping was dominated by all four endovenous treatments (EVLA, MOCA, RFA, and CAC). All five treatments were associated with similar QALYs over the 5-year time horizon of this analysis. These findings were consistent with results in the published economic evaluations.[13,95] Our findings were also consistent with those of the clinical evidence review in this report, in that patients' health-related quality of life following treatment was very similar across the treatment strategies.

There were several reasons for the similar QALYs across treatments in our evaluation. Overall, rates of retreatment on the great saphenous vein are low for all five index treatments, ranging from 1.9 to 3.4 retreatments per 100 patient-years. Furthermore, a failure of initial treatment would be corrected by retreatment, so the utility loss of treatment failure only occurs temporarily, for half the year. The model assumed that the initial treatment would not impact the selection of the retreatment, so patients who experienced retreatment would have same health-related quality of life, regardless of their treatment group. Thus, the five treatments resulted in similar QALYs over 5 years.

In the present study, we focused on the minimally invasive alternatives to surgical vein stripping, so we excluded the use of compression stockings alone. Compression therapy is a strategy to manage symptomatic varicose veins but does not treat the underlying venous insufficiency. Because sclerotherapy is not typically used for GSV closure in Ontario, we considered it not as an option for the index treatment but as an adjunct therapy and as one of the second-line therapies for retreatment, when the initial treatment fails.[111] We did not include the cost of post-treatment compression stockings. In Ontario, most patients are expected to use compression stockings after any treatment (telephone communications, Dr. David Szalay and Dr. Varun Kapila, June 2020). The cost of compression stockings is relatively low compared with the procedure costs and, currently, is not publicly funded.

Our analyses, which considered direct health care costs and overhead, showed that surgical vein stripping was dominated by all four endovenous treatments. If we were to consider additional factors, the differences in cost between surgical vein stripping and endovenous treatments could be even larger. For example, recovery time after surgical treatment is longer than for endovenous treatments, potentially leading to greater productivity loss. Also, compared with endovenous treatments, patients receiving surgical treatment may need extra preoperative assessment in preparation for general anesthesia, and they may have a higher risk of complications and deep vein thrombosis following the procedure. Furthermore, surgical approaches may have longer wait times (for operating room) than endovenous treatments. If our model were to consider the time people spent waiting for treatment, and the lower health-related quality of life they would experience during this wait, endovenous treatments would likely lead to greater QALYs gained than our analyses found, compared with surgical vein stripping. Therefore, we expect that surgical vein stripping treatment would be gradually replaced by endovenous treatments, if endovenous treatments were to become available in the publicly funded health care system.

Finally, we presented our results at the provincial level, which may not reflect the cost-effectiveness of varicose veins treatment at an individual health centre. For example, although CAC is associated with a higher cost for the device kit, it does not need the level of capital investment for equipment compared with surgery and thermal therapies, and the requirement for treatment rooms is not as high. Therefore, if a health centre has a small volume of treatments, the average cost of a CAC procedure may be lower than for RFA or ELVA in this specific setting. Also, we made assumptions about professional fees for the

four endovenous treatments in our economic analyses. If endovenous treatments are publicly funded in Ontario, physician reimbursement for performing the procedure may be similar to radiology procedures, including both professional and technical fees, and the reimbursed amount will be determined by the Ontario Health Insurance Plan.

Strengths and Limitations

Our study had the following strengths:

- Our input parameters reflect the Ontario context and were confirmed by numerous expert consultations
- We provided estimates of the economic implications of five treatment types, considering long-term costs including retreatment on the GSV and adjunct therapy for residual varicosities
- Various analyses covered many possible scenarios

The following limitations should be noted when interpreting the findings of this analysis:

- Given the variability of clinical practice in different health centres, our cost estimates from a private clinic may not precisely reflect the average resource use (e.g., nursing hours, professionals involved in each procedure) for CAC, MOCA, RFA, and EVLA in Ontario
- Due to a lack of data, we used proxy measures for health state utilities
- We did not conduct subgroup analyses (e.g., patients with more severe disease), since we did not find high-quality evidence to compare surgical vein stripping and endovenous treatments for subgroups of patients

Conclusions

Compared with surgical vein stripping, all nonthermal and thermal endovenous treatments (CAC, MOCA, RFA, and EVLA) were more effective and less costly strategies for treating people with symptomatic varicose veins. The differences in QALYs among endovenous treatments were small, which makes the results very uncertain. If we were to look at the most cost-effective strategy (at a willingness-to-pay value of less than $100,000 per QALY), EVLA is most likely to be cost-effective.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding nonthermal and thermal endovenous treatments for people with symptomatic varicose veins?

Methods

Analytic Framework

We estimated the budget impact of publicly funding nonthermal (cyanoacrylate adhesive closure [CAC], mechanochemical ablation [MOCA]) and thermal (endovenous laser ablation [EVLA] and radiofrequency ablation [RFA]) endovenous therapy using the cost difference between two scenarios: (1) current clinical practice without public funding for nonthermal or thermal endovenous therapy (the current scenario) and (2) anticipated clinical practice with public funding for nonthermal and thermal endovenous therapy (the new scenario). Figure 14 presents the budget impact model schematic.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

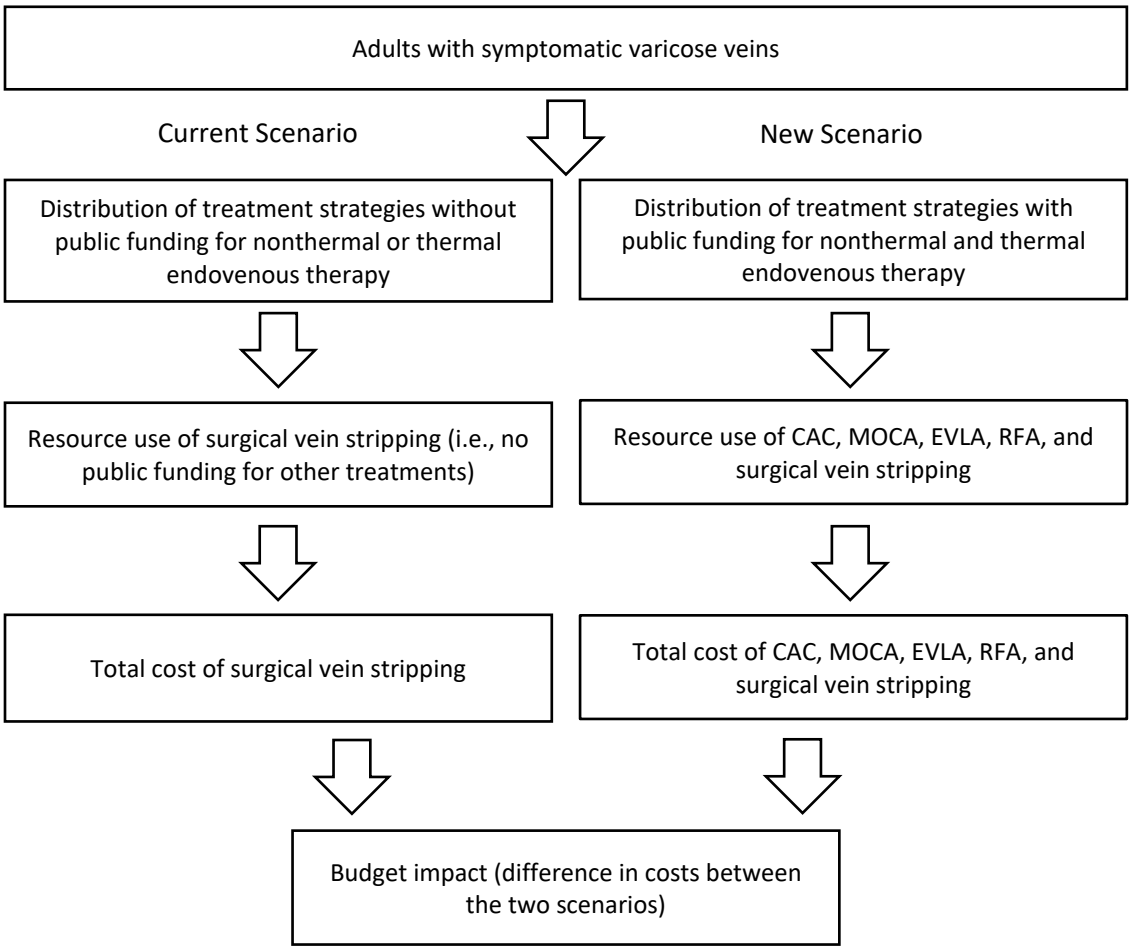

Figure 14: Schematic Model of Budget Impact, Endovenous Procedures for Symptomatic Varicose Veins

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

Key Assumptions

- In the current scenario, we expected that some people with symptomatic varicose veins would not receive surgical vein stripping due to the invasiveness of this treatment. They either would not receive treatments, or they would receive EVLA, RFA, CAC, or MOCA in private clinics. For simplicity, we assumed that the cost to the public health care system for these patients is zero
- In the new scenario, we assumed that the overall volume of treatments for symptomatic varicose veins in the saphenous veins would increase if EVLA, RFA, CAC, and MOCA were available in the publicly funded health care system

Target Population

Our target population are adults (mean age: around 55 years) presenting with symptomatic varicose veins in the saphenous veins of the legs. The majority of our target population would be those with great saphenous vein (GSV) insufficiency (with or without small saphenous vein insufficiency). The prevalence of varicose veins has been reported to be around 20% to 30% (see Background: Clinical Need and Target Population for details). The potential target population in Ontario for endovenous procedures (both nonthermal and thermal treatments) may be very large. In the present analysis, we focus on the population with medical need and do not include the use of these procedures for cosmetic purposes. Earlier recommendations by CorHealth Ontario, in 2015, on public funding of endovenous thermal ablation suggested that initial criteria for public funding should be identical to the criteria for coverage of surgical ligation and vein stripping (written communication, CorHealth Ontario, February 2020). This suggestion may be still suitable for the present budget impact analysis, as it potentially mitigates overuse of endovenous procedures for solely cosmetic reasons.

Typically, surgical procedures to treat varicose veins are conducted as day surgery. Through the IntelliHealth Ontario portal, we searched the National Ambulatory Care Reporting System (NACRS) developed by the Canadian Institute for Health Information for the volume of surgical excision of veins in the legs.[98,112] NACRS captures ambulatory care visits, day surgery, and high-cost outpatient clinics. Table 47 shows that the annual volume of the principal surgical procedures to treat varicose veins was relatively stable over a recent 5-year period, ranging from 1,811 to 2,049 per year from 2014 to 2018.

Table 47: Volume of Surgical Procedures for Varicose Veins, 2014–2018

		Number of Procedures per Year				
CCI Code	**1KR87^^, Excision Partial, Veins of Leg**	**2014**	**2015**	**2016**	**2017**	**2018**
1KR87LA	Open approach	249	269	304	380	381
1KR87WJ	Open approach with special (micro) excision technique	121	182	153	201	310
1KR87WM	Open approach with stripping technique	1,441	1,448	1,357	1,398	1,358
Total		**1,811**	**1,899**	**1,814**	**1,979**	**2,049**

Abbreviations: CCI, Canadian Classification of Health Interventions.
Note: It was expected that endovenous procedures are the potential alternatives for surgical vein stripping and other surgical treatments for symptomatic varicose veins.
Source: IntelliHealth Ontario.

We consulted several clinical experts and stakeholders about the potential size of the target population in the new scenario. They anticipated that if thermal and nonthermal endovenous treatments were publicly funded, the potential target population could increase due to the following considerations:

- Currently, some people with symptomatic varicose veins receive EVLA, RFA, CAC, or MOCA at private clinics. The volume of these procedures in private clinics is unknown. It is expected that a proportion of these people would meet the medical eligibility criteria outlined in the Schedule of Benefits[36] for publicly funded physician services in Ontario

- Some people with venous insufficiency and symptomatic varicose veins do not receive surgical vein stripping, although they are medically eligible for this treatment. Reasons are varied and include safety concerns related to general anesthesia, concerns about pain from the procedure, or acceptability of invasive surgery or resulting scars. These people would be the potential target population for the endovenous procedures
- Surgical vein stripping involves a waiting time for treatment due to availability of operating rooms, among other factors (written communication, CorHealth Ontario, February 2020). As a result, the number of people who require the surgery is likely greater than the volume of surgeries actually conducted in recent years
- When we searched IntelliHealth Ontario for the volume of all procedures (including secondary procedures) for symptomatic varicose veins, the volume was around 20% higher than the number of surgical treatments classified as principal procedures (reported in Table 47). It is expected that a proportion of people who receive surgical treatment for varicose veins as a secondary procedure would be eligible for endovenous procedures

According to the most recent data available, the volume of surgical treatments in 2017 and 2018 was around 2,000 per year (see Table 47). Based on the considerations outlined above, we estimated that the target population in the new scenario would be greater than 2,000 people per year. We also expected that endovenous procedures would be introduced into the public health care system gradually. Therefore, we estimated that the target population for all procedures in the new scenario would be 3,200 in year 1, with the volume increasing by 200 people each year to 4,000 in year 5. We used other volumes in the sensitivity analyses.

Current Intervention Mix

Based on historical data from 2014 to 2018 (Table 47), we estimated that 2,000 people with symptomatic varicose veins would receive surgical treatment each year in the current scenario.

Uptake of the New Intervention and New Intervention Mix

The endovenous procedures have a number of advantages over surgical vein stripping (see Background: Current Treatment Options and Health Technologies Under Review). We expect that, if endovenous procedures are publicly funded in Ontario, the target population for these treatments will expand and gradually replace a substantial proportion of surgical vein stripping procedures over the next few years.

To estimate the uptake of the new intervention, we considered how this redistribution of treatments would evolve. Based on the experience in Saskatchewan[106] and after consulting with stakeholders (telephone communications, Dr. David Szalay and Dr. Varun Kapila, June 2020), we estimated that the combined market share of endovenous procedures (CAC, MOCA, EVLA, and RFA) would be 70% in year 1, 80% in year 2, and 90% in years 3, 4, and 5, and that the remaining procedures would be surgical (Table 48). Given that the clinical effectiveness of endovenous procedures is generally similar, that individual patients may be more suitable for a specific treatment (owing to their unique anatomical features, age, or overall health), and that individual hospitals may adopt some but not all treatment options, it was expected that all four types of endovenous procedures will be used in Ontario in next 5 years. We expected that CAC would have the largest market share given its potential advantage[61] and patient preferences (see Preferences and Values Evidence). MOCA would have the smallest market share as currently this treatment has not been widely used in Ontario and has slightly lower clinical

effectiveness compared with other endovenous treatments (see Clinical Evidence Review). We then estimated the market share for each treatment. The corresponding volumes of treatments in the current and new scenarios can be found in Table 49.

Table 48: Market Distribution of Procedures for Symptomatic Varicose Veins in Current Scenario and New Scenario

	% of Total Volume				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Current Scenario					
Surgical procedure	100	100	100	100	100
New Scenario					
Surgical procedure	30	20	10	10	10
Endovenous procedure	70	80	90	90	90
CAC	*34*	*37*	*40*	*40*	*40*
MOCA	*1*	*3*	*5*	*5*	*5*
EVLA	*17.5*	*20*	*22.5*	*22.5*	*22.5*
RFA	*17.5*	*20*	*22.5*	*22.5*	*22.5*

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

Table 49: Volumes of Procedures for Symptomatic Varicose Veins in the Current Scenario and New Scenario

	Number of Procedures[a]					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
Surgical vein stripping	2,000	2,000	2,000	2,000	2,000	10,000
New Scenario						
CAC	1,088[a]	1,258	1,440	1,520	1,600	6,906
MOCA	32	102	180	190	200	704
EVLA	560	680	810	855	900	3,805
RFA	560	680	810	855	900	3,805
Surgical vein stripping	960	680	360	380	400	2,780
Total new scenario	**3,200**	**3,400**	**3,600**	**3,800**	**4,000**	**18,000**

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

[a]The volume of interventions was calculated from the total number of annual procedures, multiplied by the market share of the corresponding treatment (see Table 48). For example, in the new scenario, the total volume in year 1 was 3,200 and the market share of CAC was 34%, so the volume of CAC in year 1 was 1,088 (3,200 × 34%).

Resources and Costs

This analysis was conducted from the perspective of the Ontario Ministry of Health. All costs were reported in 2020 Canadian dollars.[104] Details of procedure costs have been reported in the Primary Economic Evaluation (see Table 43). Compared with index treatments, the costs of adjunct treatment and retreatment are relatively small and uncertain. Thus, in the reference case, we only included procedure costs for initial (index) treatment and excluded the cost of adjunct therapy and retreatment. In the scenario analyses, we included various cost components.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

The budget impact was calculated as the cost difference between the current scenario (no public funding for endovenous therapy) and the new scenario (public funding for nonthermal and thermal endovenous therapy) for adults with symptomatic varicose veins in Ontario. We calculated the total costs of each treatment using the average cost per patient for each treatment multiplied by the corresponding volume of the treatment per year. The total costs for each scenario was the sum of total costs for the five treatments. We calculated the annual budget impact for the next 5 years.

We also explored the budget impact in sensitivity analyses, using eight scenarios, described below. In these scenarios, we used the values of parameters shown in Tables 50 and 51, while other parameters were same as these in the reference case. Table 50 presents the average costs used in the reference case and in scenarios 1 to 3. Table 51 presents the volumes of treatments used in scenarios 4 to 8 where they differed from the reference case.

- Scenario 1: including only the direct health care costs of initial treatment (i.e., overhead cost excluded)
- Scenario 2: including the costs of initial treatment, adjunct therapy, and retreatment. For this scenario, we ran the Primary Economic Evaluation model over a 5-year time horizon and estimated the average costs (without discounting) per year for each treatment. The budget impact analysis included the cumulative impact of retreatments (up to 5 years) after the index treatment
- Scenario 3: considering lower costs for each type of endovenous procedure, at 75% of those in the reference case
- Scenario 4: including only surgical vein stripping, CAC, and MOCA in the new scenario (i.e., EVLA and RFA excluded) because the main goal of this health technology assessment is to evaluate nonthermal endovenous procedures
- Scenario 5: assuming that the volume of treatments for symptomatic varicose veins is 1.5 times (Scenario 5-1) and 2 times (Scenario 5-2) higher than in the reference case, and that the market share of each treatment remains the same as in the reference case (see Table 48). This scenario considers a potentially larger diffusion of endovenous treatments over time if they were publicly funded

- Scenario 6: assuming that the potential target population in the new scenario is the same as the current scenario, about 2,000 per year over 5 years, and that the market share of each treatment is the same as in the reference case (see Table 48)
- Scenario 7: considering a slower adoption process for endovenous procedures over 5 years. In this scenario, the market share of endovenous procedures is 40% in year 1, 50% in year 2, 60% in year 3, 70% in year 4, and 80% in year 5. The total volume of treatments for symptomatic varicose veins in this scenario remains the same as in the reference case
- Scenario 8: considering a slower (3%) annual increase in the volume of surgical vein stripping procedures in the current scenario, starting with 2,000 procedures in year 1. In the new scenario, the total volume and market distribution are the same as in the reference case

Table 50: Costs of Procedures, Reference Case and Scenarios 1 to 3

	CAC	MOCA	EVLA	RFA	Surgical Vein Stripping
Reference Case: Including Cost of Index Treatment, $[a]					
Cost per patient	2,774	2,483	2,324	2,743	3,217
Scenario 1: Including Only Direct Health Care Costs of Index Treatment, $[a]					
Cost per patient	2,372	2,081	1,720	2,139	2,412
Scenario 2: Including Costs of Index Treatment, Adjunct Treatment, and Retreatment,[b] $[a]					
Cost in year 1	2,787	2,513	2,345	2,759	3,245
Cost in year 2	29	55	51	31	55
Cost in year 3	28	53	49	30	53
Cost in year 4	27	50	46	29	51
Cost in year 5	26	48	44	28	49
Scenario 3: Lower Costs for CAC, MOCA, EVLA, and RFA, $[a]					
Cost per patient	2,081	1,862	1,743	2,057	3,217

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.
[a]In 2020 Canadian dollars.
[b]Based on the economic model in the Primary Economic Evaluation, we calculated the annual undiscounted cost over 5 years for each treatment.

Table 51: Volumes of Procedures, Scenarios 4 to 8

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario 4: New Scenario Includes Only CAC, MOCA, and Surgical Vein Stripping						
CAC	2,080	2,380	2,700	2,850	3,000	13,010
MOCA	160	340	540	570	600	2,210
Surgical vein stripping	960	680	360	380	400	2,780
Total	3,200	3,400	3,600	3,800	4,000	18,000
Scenario 5-1: Volume of Procedures in New Scenario is 1.5 times Higher Than in Reference Case						
CAC	1,632	1,887	2,160	2,280	2,400	10,359
MOCA	48	153	270	285	300	1,056
EVLA	840	1,020	1,215	1,283	1,350	5,708
RFA	840	1,020	1,215	1,282	1,350	5,707
Surgical vein stripping	1,440	1,020	540	570	600	4,170
Total	4,800	5,100	5,400	5,700	6,000	27,000
Scenario 5-2: Volume of Procedures in New Scenario is 2 times Higher Than in Reference Case						
CAC	2,176	2,516	2,880	3,040	3,200	13,812
MOCA	64	204	360	380	400	1,408
EVLA	1,120	1,360	1,620	1,710	1,800	7,610
RFA	1,120	1,360	1,620	1,710	1,800	7,610
Surgical vein stripping	1,920	1,360	720	760	800	5,560
Total	6,400	6,800	7,200	7,600	8,000	36,000
Scenario 6: Volume of Procedures in New Scenario is Same as in Current Scenario						
CAC	680	740	800	800	800	3,820
MOCA	20	60	100	100	100	380
EVLA	350	400	450	450	450	2,100
RFA	350	400	450	450	450	2,100
Surgical vein stripping	600	400	200	200	200	1,600
Total	2,000	2,000	2,000	2,000	2,000	10,000
Scenario 7: Slower Adoption of Endovenous Procedures in New Scenario						
CAC	608	782	972	1,178	1,400	4,940
MOCA	32	68	108	152	200	560
EVLA	320	425	540	665	800	2,750
RFA	320	425	540	665	800	2,750
Surgical vein stripping	1,920	1,700	1,440	1,140	800	7,000
Total	3,200	3,400	3,600	3,800	4,000	18,000
Scenario 8: 3% Annual Increase in Surgical Procedures in Current Scenario						
Surgical vein stripping	2,000	2,060	2,122	2,185	2,251	10,618

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

Results

Reference Case

Table 52 presents the projected total costs over 5 years of the new scenario and current scenario in our reference case. The budget impact of publicly funding endovenous treatments (CAC, MOCA, EVLA, and RFA) was $2.59 million in year 1 and increased to $4.35 million in year 5. The total 5-year budget impact was around $17 million.

We further estimated the budget impact for three cost categories: health care (e.g., hospital costs and professional fees), device costs for endovenous treatment (device kit, disposable materials, and equipment), and overhead costs (Appendix 6, Table A15). Publicly funding endovenous procedures would lead to savings of $5.91 million in health care cost over 5 years, but the budget for endovenous treatment devices would increase $21.02 million over 5 years.

It should also be noted that we assumed funding for endovenous procedures would increase the total number of people receiving treatment over 5 years, from 10,000 procedures in the current scenario to 18,000 in the new scenario (see Table 49). Assuming that CAC would have the largest market share among the four endovenous procedures, we found that the total 5-year costs for CAC would be $19.16 million in the new scenario (Table 52).

Table 52: Budget Impact Analysis Results, Endovenous Procedures for Varicose Veins, Reference Case

	Budget Impact, $ Million [a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario	**6.43**	**6.43**	**6.43**	**6.43**	**6.43**	**32.17**
Surgical vein stripping	6.43	6.43	6.43	6.43	6.43	32.17
New scenario	**9.02**	**9.38**	**9.70**	**10.24**	**10.78**	**49.13**
CAC	*3.02*	*3.49*	*3.99*	*4.22*	*4.44*	*19.16*
MOCA	*0.08*	*0.25*	*0.45*	*0.47*	*0.50*	*1.75*
EVLA	*1.30*	*1.58*	*1.88*	*1.99*	*2.09*	*8.84*
RFA	*1.54*	*1.87*	*2.22*	*2.35*	*2.47*	*10.44*
Surgical vein stripping	*3.09*	*2.19*	*1.16*	*1.22*	*1.29*	*8.94*
Budget impact	**2.59**	**2.94**	**3.27**	**3.81**	**4.35**	**16.96**

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

[a]In 2020 Canadian dollars.

[b]Some numbers may appear inexact due to rounding.

Sensitivity Analyses

Table 53 presents the results of the eight scenarios in our sensitivity analyses. Compared with the reference case, funding endovenous procedures would have a greater budget impact if the target populations were larger (Scenarios 5-1 and 5-2). Compared with the reference case, funding endovenous procedures would have a smaller budget impact if only direct health care costs (i.e., excluding overhead costs) were considered (Scenario 1) or if the per-procedure costs for CAC, MOCA, EVLA and RFA were lower (e.g., discounted prices for device kits and equipment after negotiating with manufacturers; scenario 3). When the overall volume of treatments in the new scenario was the same as in the current scenario, publicly funding endovenous procedures would lead to cost savings because endovenous procedures cost less than surgical veins stripping (Scenario 6).

Table 53: Budget Impact Analysis Results, Endovenous Procedures for Varicose Veins, Sensitivity Analyses

	Budget Impact, $ Million [a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Reference Case						
Budget impact	**2.59**	**2.94**	**3.27**	**3.81**	**4.35**	**16.96**
Scenario 1: Including Only Direct Health Care Costs of Index Treatment						
Current scenario	4.82	4.82	4.82	4.82	4.82	24.12
Surgical vein stripping	*4.82*	*4.82*	*4.82*	*4.82*	*4.82*	*24.12*
New scenario	7.12	7.46	7.78	8.22	8.65	39.23
CAC	*2.58*	*2.98*	*3.42*	*3.61*	*3.80*	*16.38*
MOCA	*0.07*	*0.21*	*0.37*	*0.40*	*0.42*	*1.47*
EVLA	*0.96*	*1.17*	*1.39*	*1.47*	*1.55*	*6.54*
RFA	*1.20*	*1.45*	*1.73*	*1.83*	*1.93*	*8.14*
Surgical vein stripping	*2.32*	*1.64*	*0.87*	*0.92*	*0.96*	*6.71*
Budget impact	**2.30**	**2.64**	**2.96**	**3.39**	**3.83**	**15.11**
Scenario 2: Including Costs of Index Treatment, Adjunct Treatment, and Retreatment						
Current scenario	6.49	6.60	6.71	6.81	6.90	33.50
Surgical vein stripping	*6.49*	*6.60*	*6.71*	*6.81*	*6.90*	*33.50*
New scenario	9.09	9.57	10.03	10.70	11.37	50.77
CAC	*3.03*	*3.54*	*4.08*	*4.34*	*4.61*	*19.60*
MOCA	*0.08*	*0.26*	*0.46*	*0.49*	*0.53*	*1.82*
EVLA	*1.31*	*1.62*	*1.96*	*2.11*	*2.25*	*9.25*
RFA	*1.55*	*1.89*	*2.27*	*2.42*	*2.57*	*10.70*
Surgical vein stripping	*3.12*	*2.26*	*1.26*	*1.34*	*1.42*	*9.39*
Budget impact	**2.60**	**2.97**	**3.33**	**3.90**	**4.47**	**17.26**

Scenario	Budget Impact, $ Million [a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario 3[c]: Lower Costs for CAC, MOCA, EVLA, and RFA						
New scenario	7.54	7.58	7.57	7.99	8.41	39.08
CAC	*2.26*	*2.62*	*3.00*	*3.16*	*3.33*	*14.37*
MOCA	*0.06*	*0.19*	*0.34*	*0.35*	*0.37*	*1.31*
EVLA	*0.98*	*1.19*	*1.41*	*1.49*	*1.57*	*6.63*
RFA	*1.15*	*1.40*	*1.67*	*1.76*	*1.85*	*7.83*
Surgical vein stripping	*3.09*	*2.19*	*1.16*	*1.22*	*1.29*	*8.94*
Budget impact	**1.11**	**1.14**	**1.13**	**1.55**	**1.97**	**6.91**
Scenario 4[c]: New Scenario Includes Only CAC, MOCA, and Surgical Vein Stripping						
New scenario	9.26	9.63	9.99	10.54	11.10	50.52
CAC	*5.77*	*6.60*	*7.49*	*7.91*	*8.32*	*36.09*
MOCA	*0.40*	*0.84*	*1.34*	*1.42*	*1.49*	*5.49*
Surgical vein stripping	*3.09*	*2.19*	*1.16*	*1.22*	*1.29*	*8.94*
Budget impact	**2.82**	**3.20**	**3.55**	**4.11**	**4.66**	**18.35**
Scenario 5-1[c]: Volume of Procedures in New Scenario is 1.5 Times Higher Than in Reference Case						
New scenario	13.54	14.06	14.56	15.36	16.17	73.69
CAC	*4.53*	*5.23*	*5.99*	*6.32*	*6.66*	*28.74*
MOCA	*0.12*	*0.38*	*0.67*	*0.71*	*0.74*	*2.62*
EVLA	*1.95*	*2.37*	*2.82*	*2.98*	*3.14*	*13.26*
RFA	*2.30*	*2.80*	*3.33*	*3.52*	*3.70*	*15.66*
Surgical vein stripping	*4.63*	*3.28*	*1.74*	*1.83*	*1.93*	*13.41*
Budget impact	**7.10**	**7.63**	**8.12**	**8.93**	**9.74**	**41.52**
Scenario 5-2[c]: Volume of Procedures in New Scenario is 2 Times Higher Than in Reference Case						
New scenario	18.05	18.75	19.41	20.49	21.56	98.26
CAC	*6.04*	*6.98*	*7.99*	*8.43*	*8.88*	*38.31*
MOCA	*0.16*	*0.51*	*0.89*	*0.94*	*0.99*	*3.50*
EVLA	*2.60*	*3.16*	*3.76*	*3.97*	*4.18*	*17.69*
RFA	*3.07*	*3.73*	*4.44*	*4.69*	*4.94*	*20.87*
Surgical vein stripping	*6.18*	*4.38*	*2.32*	*2.44*	*2.57*	*17.89*
Budget impact	**11.61**	**12.32**	**12.97**	**14.05**	**15.13**	**66.09**

Scenario	Budget Impact, $ Million [a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario 6[c]: Volume of Procedures in New Scenario is Same as in Current Scenario						
New scenario	5.64	5.52	5.39	5.39	5.39	27.33
CAC	*1.89*	*2.05*	*2.22*	*2.22*	*2.22*	*10.60*
MOCA	*0.05*	*0.15*	*0.25*	*0.25*	*0.25*	*0.94*
EVLA	*0.81*	*0.93*	*1.05*	*1.05*	*1.05*	*4.88*
RFA	*0.96*	*1.10*	*1.23*	*1.23*	*1.23*	*5.76*
Surgical vein stripping	*1.93*	*1.29*	*0.64*	*0.64*	*0.64*	*5.15*
Budget impact	**−0.79**	**−0.92**	**−1.04**	**−1.04**	**−1.04**	**−4.84**
Scenario 7[c]: Slower Adoption of Endovenous Procedures in New Scenario						
New scenario	9.56	9.96	10.33	10.68	11.01	51.55
CAC	*1.69*	*2.17*	*2.70*	*3.27*	*3.88*	*13.70*
MOCA	*0.08*	*0.17*	*0.27*	*0.38*	*0.50*	*1.39*
EVLA	*0.74*	*0.99*	*1.25*	*1.55*	*1.86*	*6.39*
RFA	*0.88*	*1.17*	*1.48*	*1.82*	*2.19*	*7.54*
Surgical vein stripping	*6.18*	*5.47*	*4.63*	*3.67*	*2.57*	*22.52*
Budget impact	**3.13**	**3.53**	**3.90**	**4.25**	**4.57**	**19.38**
Scenario 8: 3% Annual Increase in Surgical Procedures in Current Scenario						
Current scenario	6.43	6.63	6.83	7.03	7.24	34.16
Surgical vein stripping	*6.43*	*6.63*	*6.83*	*7.03*	*7.24*	*34.16*
Budget impact	**2.59**	**2.75**	**2.88**	**3.21**	**3.54**	**14.97**

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.
[a]In 2020 Canadian dollars.
[b]Some numbers may appear inexact due to rounding.
[c]The cost of current scenario was same as the reference case, so these cost are not presented in this table.

Discussion

Our analysis shows that publicly funding endovenous treatments for people with symptomatic varicose veins would lead to an annual budget increase of between $2.59 million and $4.35 million over 5 years. Although the per-procedure cost of endovenous treatments is lower than for surgical vein stripping, funding endovenous treatments would likely be associated with an increased volume of varicose vein procedures, resulting in the increased budget.

We limited our target population to people with medical need for varicose vein treatment. Although it is difficult to strictly distinguish medical need from cosmetic reasons, the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification is used to assess severity of venous disease and includes some objectively observable indicators of medical need. Clinicians can judge the needs of individual patients based on their overall clinical picture (e.g., the person's symptoms, comorbidities, anatomy, clinical

history, and the impact of varicose veins on their ability to function and quality of life). If we were to include people with only a cosmetic need for treatment, the size of the target population for publicly funded endovenous treatments would substantially increase.

Our primary economic evaluation showed that, compared with endovenous treatments, surgical vein stripping has higher costs and lower impacts on health (as measured by quality-adjusted life-years). Also, patients tend to prefer endovenous treatments over surgical vein stripping (see Preferences and Values Evidence). Therefore, we can expect that the market share of surgical vein stripping will decrease over time if endovenous treatments are publicly funded. But surgical approaches cannot be fully replaced by endovenous treatments because surgical treatment may be more suitable for people with certain conditions, particularly those with anatomical tortuosity (very twisted veins), very large veins (diameter ~ > 1 cm), or allergy to cyanoacrylate glue (telephone communication, Dr. Varun Kapila, June 2020). With this in mind, we acknowledge that patient characteristics for surgical vein stripping and endovenous treatments are potentially different. However, due to a lack of reliable data that would allow us to estimate costs according to different patient characteristics, we used the same procedure costs for everyone who could be eligible for varicose veins treatments.

Butt and Kopriva, 2018[106] reported that the volume of treatments for varicosity of the great saphenous vein did not increase after public funding of RFA and EVLA began in a health centre in Saskatchewan. The average volume of GSV interventions was around 90 cases per year in their health centre, which covered a regional population of 230,000 people and also provided referral services for 450,000 people in Saskatchewan. The volumes of surgical vein stripping, RFA, and EVLA at the provincial level in Saskatchewan were unknown. Extrapolating the experience of one hospital in another province to Ontario at the provincial level is challenging. If endovenous procedures were publicly funded in Ontario, the total volumes of procedures for symptomatic varicose veins in hospitals currently providing surgical vein stripping may not change (i.e., similar to the experience of one hospital in Saskatchewan).[106] At the same time, we expect that more health care facilities (e.g., some small hospitals or clinics that currently do not manage people with venous insufficiency) would provide endovenous procedures. Thus, the total provincial volumes are likely to increase with public funding of endovenous procedures. Also of note, the current volumes of varicose vein procedures may reflect constraints in the health system's capacity as opposed to true clinical need. Given all the uncertainties around estimating the size of the target population for these procedures, we analyzed several scenarios to address the possibility that endovenous treatments would see greater diffusion in the province within the first 5 years of being publicly funded.

Strengths and Limitations

Our study had the following strengths:

- Our input parameters reflect the Ontario context and were confirmed in numerous expert consultations
- Various analyses covered many possible scenarios, and the cost estimates we used can easily be extended for further analysis

The following limitations should be noted when interpreting the findings of this analysis:

- The volume of surgical vein stripping from historical data may not entirely reflect current and future medical need in the Ontario population

- The volumes of endovenous treatments in private clinics are unknown
- The projected volumes of treatment in the new scenario were based on expert opinion and may have large uncertainty

Conclusions

If thermal and nonthermal endovenous treatments are publicly funded in Ontario for adults with symptomatic varicose veins, the potential target population could increase considerably. Assuming an 80% increase in the number of eligible people, we estimate that the annual budget impact would range from $2.59 million in year 1 to $4.35 million in year 5, and that the total 5-year budget impact would be around $17 million.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience with varicose veins and potential treatment options, such as nonthermal endovenous treatments.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[113-115] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are often inadequately explored in the published literature, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we directly engaged people, through interviews, to examine the preferences and values of people who have lived experience with varicose veins and who may consider seeking a treatment option such as nonthermal endovenous treatments.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with varicose veins and who may have received nonthermal endovenous treatments. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with lived experience with varicose veins.[116] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[117-120] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations and clinical experts to spread the word about this

engagement activity and to contact people with experience with varicose veins and, potentially, nonthermal endovenous treatment.

Inclusion Criteria

We sought to speak with people with lived experience of varicose veins and nonthermal treatments, including mechanochemical ablation (MOCA) and cyanoacrylate adhesive closure (CAC), or who may seek out these treatments in the future. Participants did not need to have direct experience with these procedures to participate.

Exclusion Criteria

We did not set exclusion criteria for people who otherwise met our inclusion criteria.

Participants

For this project, we spoke with 13 people with lived experience of varicose veins. Seven participants had received CAC treatment at private clinics, while the remaining six people had tried other treatment options. Because MOCA is rarely performed in Ontario, we were unable to speak with anyone who had used this procedure. Participants were mainly located in southern Ontario; however, two people lived in northern areas of the province.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 7), if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 15 to 30 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[121] Questions focused on the impact of varicose veins on people's quality of life and their experiences with various treatment options. Participants were also asked specifically about their experiences with CAC treatment, if applicable, including their perceptions of the benefits or limitations of this procedure and its impact. See Appendix 8 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[122,123] We used the qualitative data analysis software program NVivo[17,124] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of varicose veins on a person's quality of life and patients' perceptions of nonthermal endovenous procedures as a potential treatment.

Results

DEVELOPING AND LIVING WITH VARICOSE VEINS

During interviews, the majority of patients reported that their varicose veins began during pregnancy or shortly thereafter. Often, varicose veins had not been an issue prior to the pregnancy and had not been a condition with which participants were overly concerned. Participants were well-informed about the causes of varicose veins, reporting that they were a result of blood flow insufficiency brought on by the physical changes of pregnancy:

> *So the first, I'd say, five births there was no real varicose veins … But as I had more pregnancies, then veins started to be more noticeable and where, particularly during pregnancy, it was bulging up. It would get a little bit itchy.*
>
> *So, with my first pregnancy when I was 23, I started having pain in the back of my left calf and that's where my varicose veins kind of crept up. And now I have sort of a ropey vein back there.*
>
> *I remember speaking to the obstetrician about it. And he says, it probably runs in your family and you know you've had three consecutive pregnancies. So it's been hard on your system. So the valves and the flow couldn't keep up, because when women are pregnant we're heavier, so there's a lot more blood flow going on.*

In talking about why or when they developed varicose veins, some participants mentioned that varicose veins seemed to be a familial issue, as they had family members with the condition. One person also reported that his varicose veins were caused by physical injury to his legs due to many years of sporting activities:

> *So just as a kid, I would say that varicose veins runs in our family. My dad had them, my mom had them. So I remember as a grade nine, on my right leg, having some obvious vein. It didn't evolve or anything like that, but just noticing, "Oh, I've got a vein there that my friends don't have."*
>
> *I went on to play university football for five years after [a leg injury] ... and that involved, you know, putting on about 50 pounds and playing at that level and then losing about 50 pounds. And so my body and my legs went through, I guess, quite a bit of stress … I had my first you know, venogram and all the deeper veins looked fine but the protruding varicose veins were very prominent. And I was only in my 20s.*
>
> *Varicose veins, it run in the family, so I've got the hereditary factor. I've got the occupational hazard because I taught for four decades. And then four pregnancies was when it really began to show up. Also, weight isn't my forte so I've got the weight issue as well, all playing a role to have the varicose veins.*

No matter the cause, participants reported consistent features of this condition. Firstly, many participants commented on the physical appearance of their varicose veins. They used descriptions such as "bulging" or described a distinct change in colour around the veins or at a certain part of the leg. Participants also reported developing varicose veins in various parts of the leg, from the ankle or calf up to the groin area:

> *Although I didn't have big bulging veins, I certainly did have some spots that were swollen and protruding. But overall, you know, I didn't have those really ugly ones, but my one ankle the one summer was completely … it was gross. I couldn't put a shoe on, it for sure was protruding. I had one under my knee that was pretty bad.*
>
> *I'd be in shorts in the summertime … It's not like I think I should be a leg model or anything; I wasn't super self-conscious of it. But people or even family, relatives or what have you, would look at my legs were like, "Oh my goodness, what's going on there??" That kind of thing would happen frequently throughout the summer and I'd joke that if I cut the grass in shorts all the kids in the neighborhood would go screaming running away.*
>
> *But I do have one extremely large, big one right from my hip down to my knee that bulges even through your pants or anything. It's very visible … but I also have a lot of the spider veins around the ankles as well.*

Secondly, participants consistently reported pain and sensations of achiness or weariness caused by their varicose veins. These sensations could wax and wane depending on daily conditions, but they were reported to be very common. Additionally, some participants complained of swelling caused by the venous insufficiency underlying their varicose veins and sensations of heat or tenderness in the regions where the varicose veins were prominent:

> *[I] had tons of pain, massive amounts of swelling, no ulcers. But it's like it was a daily thing I had to kind of deal with.*
>
> *And for now almost 30 years I've had aching pain there, especially when I have my period. It seems to be associated with my cycle. I don't know why that is but there you go.*
>
> *The rest of [my legs] are still painful, sensitive, fatiguing, throbbing. My legs were always frozen like they were just so cold. And I didn't know if it was because the blood just wasn't returning, circulating, I guess, properly.*

IMPACT ON QUALITY OF LIFE

Naturally, the pain, swelling, and soreness from varicose veins negatively affected participants' quality of life. In our interviews, people described how these symptoms often resulted in a reduced level of activity and alterations to their daily routines. Working could be more difficult, at times, due to pain arising from sitting or standing too long, which can exacerbate the effects of varicose veins. Some participants reported having to take precautions or adjust their schedules if they anticipated long trips or activities which would require staying in one place for an extended time. For those with more severe cases of varicose veins, even sleeping next to their partners could be a challenge due to pain from just being touched:

> *They affected my quality of life; I couldn't go to work every day.*
>
> *I do need to get something done. It affects my job. It affects my mobility. I can't work out, I can't run, I can't do activities with the kids. [I'm] always concerned about being able to put my feet up if necessary.*

> *But I absolutely had to get up and walk around, always set timers. I had to get a sit-stand desk. I do a lot of sitting for my job. And again, I'd just have to be prepared; if I traveled, I'd be swollen so of course I would ice or make sure to get lots of activity in, that sort of thing, to keep things moving as well.*
>
> *And it was just getting so uncomfortable to the point where, literally, I would go to bed, pull my sheets up, and I could feel my sheets on my veins. Or if my husband sort of moved over and kicked a leg over me, I could have killed him because it just hurt so bad, right? It was like, "Don't touch my leg, don't come near my leg!" They hurt so much.*

Participants reported trying many things on their own to alleviate some of the pain or soreness caused by varicose veins. This could include icing their legs, elevating them, increasing movement and exercise, or herbal remedies in an attempt to increase blood flow and reduce pain. These methods of self-care were moderately successful, participants reported, but were not permanent solutions and could be impractical, depending on the situation:

> *And if I walk a little bit, I felt a little bit better. But after, I … went back to sit in front of the computer for about 40 or 45 minutes, the heavier feelings still came back.*
>
> *By my third, last pregnancy, I was putting my legs up more. Like a month before the baby was born, I would put them up, I would ice them … or put a cool pack on it. [I was] just finding more discomfort.*
>
> *I stretch, I walk during the day regularly … almost every 40 or 45 minutes. It helps but I felt it's getting worse and worse.*
>
> *I found those treatments were also helpful but it was only helpful a couple of hours after the treatment. The pain, the aches, and the discomfort still come back.*

The challenges caused by varicose veins and the negative impact on their quality of life led to frustration, participants reported. Many recounted the number of years they had dealt with varicose veins and the emotions of dismay and frustration that arose after such a long time of living with this condition:

> *So years later, I started to get a little fed up because my legs were becoming more painful. They were throbbing, very sensitive.*
>
> *You know, if I'm planning a trip or I have a commitment or there's a social thing, it's just on my mind that there's this thing I have to bear. Which is honestly, so annoying to me and, yeah … it's so annoying to me.*

Additionally, some participants reported concerns about the medical risks associated with increasingly severe varicose veins. In doing their own research and speaking with their doctors, participants were aware that worsening varicose veins may lead to complications such as ulcers or deep vein thrombosis (DVT), a blood clot that can become life-threatening. These potential risks caused anxiety and fear and led some participants to change their activities:

> *The doctor says to me, "I wouldn't do those types of [activities] … Don't put yourself at risk because, with varicose veins, you have a higher rate at developing a DVT because your veins are more exposed than other people." So I'm thinking, okay, now I've got to limit my physical activity.*
>
> *It kind of felt like it was throbbing, sometimes they would feel itchy, but that's not a problem. But just this throbbing, [being] tired, I need to keep my legs up. And just this constant fear; so this is where you're wondering, "Is this something that should be covered [with a compression stocking]?" Just this fear: "Am I going to die because of [a DVT] … A clot is going to make me die?"*

Fears of these complications, along with concerns about the ongoing impact of living with varicose veins, spurred participants to seek further treatment. They expressed hope that there could be a permanent solution that would relieve their symptoms and reduce the risk of future problems:

> *And then my leg was hot. Again, I'm in the hospital checking for a DVT. So, after that happened twice, I was quite frustrated and I thought, there has to be a different route to fixing this. Because it's impacting my quality of life.*
>
> *My one leg in particular started to become quite dark, almost black, near the ankle. And I thought, you know what, I'm young, I need to investigate this, I need to deal with this.*
>
> *I mean, there was no specific health issue, it was more prophylactic, the idea that there could be issues down the road. And as you start getting a little older, you start aging ... I like to take care of things that remove some risks that I might otherwise encounter as I age*.

THE CARE JOURNEY

In seeking treatment for varicose veins, most participants were motivated by the prospect of relief from the physical pain. While some acknowledged they had cosmetic concerns as well, this seemed to be a secondary consideration, viewed as less important than other symptoms. However, the balance of medical and cosmetic motivations was unique for each individual, and participants expressed a range of views:

> *But my motivation was not the cosmetic part, my motivation was the pain and the fact that I was freaked out when [the doctor] told me my legs could one day ulcer and I'd have these open sores. And I thought, "Yeah, no, that's not happening, I need to deal with this now," right? So that was my motivation.*
>
> *I'm at the point where it's not just an aesthetic consideration, it actually does have some serious health [considerations] … If I delay, I could not be doing that myself a good favour.*
>
> *I've got spider veins. I don't care. It's not how it looks; I could deal with this, I really, really could. It's how it feels. I have throbbing pain in the back of my leg. It's not right that I have to walk around with that. If I had [pain] anywhere else in my body, like in my teeth even, I don't know, I just feel like it'd be a priority.*

In seeking medical care, most participants reported first seeing their family doctor, who would sometimes refer them to a specialist. Typically, the first treatment option offered was compression

stockings, to help control swelling and increase blood flow. Participants generally reported that compression stockings could be effective, at least temporarily, but using them was often challenging and uncomfortable: they could be hard to get on and off and be hot to wear. While some people found the stockings helpful, others reported that their treatment adherence was low:

> *I stand a lot, I'm in the kitchen a lot, I'm walking with the kids. I sit a lot, but I just noticed that [compression stockings] kind of gave me a bit of a spring in my step. So that was probably recommended about pregnancy 10 and I just found those helpful.*

> *Where I bought them wasn't terribly helpful, and the ones I bought were a nightmare to try to put on. To the point where it was taking me like 40 minutes to get a set of socks on, and I would be like, sweating profusely. And I thought to myself, something's wrong. There's no way elderly people can [put them on] because, you know, I'm 40 years old, and I can't ... so I kind of gave up on those …*

> *I talked to my family doctor and I asked him if I can use the compression stockings. He prescribed that for me so I use that sometimes during the day. I found it is a little helpful, but the conditions I feel came back; the heavier feeling and the discomfort still come back.*

Participants reported that they often agreed to use compression stockings because their doctor recommended this treatment and because the cost was low. The cost was often covered by private insurance or publicly covered when prescribed by their family doctor. When it came to other treatments for varicose veins, however, the cost of these procedures became a factor in participants' treatment decision-making, as we explore further, below.

TREATMENT DECISION-MAKING

In attempting to find treatment for their varicose veins, participants consulted with their family doctors and specialists, as well as friends and colleagues, and did their own research. The amount of information about the range of treatments available varied among participants, with some expressing frustration that their doctors did not inform them about all potential treatments for varicose veins:

> *As you know with anything, as you start to have problems with something, you start engaging in conversations with people, and a friend of mine had had … well I'd met multiple people who'd had different [treatments].*

> *My family doc, he recommended compression stockings, he gave me a prescription. I don't remember him ever raising any alternative to [surgical vein] stripping.*

> *I remember being actually quite surprised when I moved to Ontario in 2014 and my new doc sort of said, "No, there's alternatives that don't involve that kind of surgery." So I wasn't aware of the alternatives until I came to Ontario and my doctor had suggested that there were alternatives to explore.*

> *Actually, I didn't approach my family doctor at all … I've got dietician friends in high places, so I talked to them. And then I also have a dermatologist who does not do vein work, but she referred me to the exact same person. And he was the only one that she would recommend, and my friend had the laser done [there]. So that's where I wanted to go.*

Participants reported learning that some varicose vein treatments are not covered by the Ontario Health Insurance Plan (OHIP). While OHIP covers compression stockings and vein stripping surgery, endovenous treatments such as sclerotherapy, laser ablation, and CAC all require patients to pay hundreds or thousands of dollars out-of-pocket. Some people said they simply could not afford those treatments, as much as they might want them:

> *Laser wouldn't be an option [for me], just because it's so expensive. I think it's in the realm of a couple of thousands of dollars for that. It wouldn't been an option.*
>
> *The people who can't afford it are the people who need it. I can't afford $8,000, I have three kids.*
>
> *But again, I have to say that the fact that this [any nonsurgical treatment] is not publicly covered is why [treating my varicose veins] has been punted and punted and not addressed, right?*

Participants reported knowing that surgical vein stripping was covered by OHIP, so it was a low-cost alternative to privately provided services. Participants who had received surgical vein stripping reported that it was largely successful: it alleviated their varicose veins issues, though it did require some recovery time:

> *I mean, surgery's never fun but the second one I found it took me much longer to heal, but I'm 15 years older than I was before and every surgery's a bit different. So, yeah, you're probably off your feet for probably a good two weeks. I mean, you're moving around, but you're not back to normal activity probably for a good two weeks and then it's a couple of months of slow gradual improvement, but you can maintain your daily activities after that.*
>
> *If I wasn't being a teacher, I would definitely have to take a good two weeks off because you just don't heal properly, right, and then what was the point?*

However, many participants reported feeling anxious about or resistant to surgical treatment, even though it would not require out-of-pocket payment. Conversations with friends or colleagues who had had (or knew of) a poor experience with this treatment resulted in a great deal of hesitation. One participant even reported a conversation with the surgeon who recommended against surgical vein stripping:

> *"You are eligible for coverage," he [the surgeon] said, "but I only strip them. So I do the invasive surgery where we rip them out basically." He said to me, "Honestly ... if you can afford it, I don't suggest you do it this route." He said, "I'm happy to do it for you, but if you can afford it I would go with the laser."*
>
> *So one of my girlfriends, she had had her veins stripped and she said it was a dreadful procedure. She said it was very painful. Yes, it's free, but, you know, when I was talking with her she's like, "You could be waiting two years." I don't know if that's accurate, but she said "You could be waiting two years for surgery because it's the free option."*
>
> *Just talking to different people, it was like if you choose the free one, just the thought of it sounds … it sounds awful, disgusting. It just feels very violent, as far as the procedure.*

> *I don't really know how much money it costs for them to do the surgery, the stripping one, but just in general, if that one could be just eliminated as an option I think most women would be a lot happier. It just sounds so invasive mentally.*

Another factor in some participants decision-making was the relatively long recovery time after surgical vein stripping, which could require days or weeks away from work and their other usual activities. For people who were employed or whose daily activities could not accommodate this downtime, this surgery did not feel like a reasonable option:

> *And I didn't want surgery – I couldn't have that downtime. So the eight weeks or whatever it was quoted at, I needed something that I could continue to work and function and move forward.*

> *Oh, I think I vaguely remember that [their recovery time after vein stripping] and thinking, well, there's no way I can be off my feet not doing stuff for weeks and weeks, like it was weeks, at least, if not even more than that.*

> *So then I got a referral [for surgical vein stripping] because it's OHIP-funded through the doctor. Went to [local] hospital. Spoke to one of the main surgeons there. He could have been the chief of surgery for vascular department and the only offer was the stripping and the recovery time, I'm a business owner, so the recovery time is horrendous. You know, I don't have EI. I don't have any benefits. And then I thought, this is crazy. I can't afford that downtime.*

Therefore, some participants reported that, despite cost being a factor in their decision-making, the downsides of low-cost treatment options, such as compression stockings or vein stripping surgery, were too great. They felt that the cost of the recovery time needed after surgical vein stripping would outweigh the cost of privately provided treatments, so they began to explore those options:

> *But I also recognize that, yeah, I could have had it for free, but that would have meant significant recovery time, that would have meant potential nerve damage. Those were just risks I wasn't willing to take when I'm a young mom who's working. I wanted to be back on my feet as soon as possible, right?*

> *Well, there's multiple reasons. Number one, the time I would have had to take off work would have far outweighed the costs of the surgery. So … it was a cost savings to actually pay for it.*

Participants also reported mixed experiences dealing with private clinics for varicose vein treatment and the perceived pressure of having treatment options "sold" to them:

> *I was recruited [referred] to this guy, I guess it was two years ago. Yes, but it was $4,000 for one leg [for CAC] and he recommended that I should maybe do both legs. As one would in a private clinic, I'm sorry. But I mean, I went with a very open mind, but I had no idea what it was going to cost.*

> *Some information that would actually illuminate which kinds of treatment might be helpful for me. But instead, of course, the conclusion of the assessment was: You should do this procedure and then I was presented with a shiny brochure and the flyers and was told, "You know, I could work out some financing" and I was like, "Okay, so what are we talking about?" and I have it in front of me: cost per leg, $4,000 [for CAC]. So I can't afford that. I support a family. I live in*

Toronto. Like it's just not realistic and I have no benefits to help offset the missed work and everything else. So it's just not at all … it's not an option for me.

EXPERIENCE WITH PRIVATELY PROVIDED TREATMENTS

Sclerotherapy

At private clinics, sclerotherapy injections were the primary treatment that participants explored. They hoped that this relatively noninvasive process would ease the physical manifestations of varicose veins and relieve some of the negative symptoms. Among participants who had experienced this treatment, reviews of sclerotherapy were mixed; some people felt that it helped cosmetically and may have relieved some pain and soreness temporarily, while others felt that they did not receive any lasting success from the injections:

And the issue with that [the sclerotherapy treatments] was, although in some cases it was cosmetically looking better, it was not feeling any better. And actually I experienced some permanent bruising from those procedures.

I'm a bit wary of being injected with anything, and I don't know that I'd describe it as a high level of concern, it was just, I wanted information about that and, in addition, I got allayed—whatever trepidation or whatever concern I might have had—and it seemed pretty straightforward … And then you notice that it's pretty amazing that the big ugly vein that you've been sort of living with is kind of disappearing in front of your eyes. I guess my concern was … I do remember this, where's all that blood going?

[Sclerotherapy injections] helped in the very short term ... it could [get] worse in other areas. It killed the small little vessels, but it got worse in higher, bigger areas.

But it's been a few years and [my] legs look great … they don't look like the same legs that I had before the treatments.

Thermal and Nonthermal Options

Other treatments options provided by private clinics were laser ablation and CAC (known by the brand name VenaSeal, for example). While laser ablation seems to be more common than CAC across the province, participants interviewed expressed some hesitation and fear about laser ablation because of its thermal nature. And while CAC was reported to be slightly more expensive, participants felt that the relatively benign nature of this procedure made it a good choice for treatment, considering all the decision-making factors discussed thus far:

I'd heard about the laser and it just seemed … I don't know, just the thought of burning veins … I just thought, "What if it hits a nerve?" I just felt very scared of that option.

The cost increase from the laser to the VenaSeal, the glue, wasn't that much more. So if you're spending thousands anyway you might as well spend a few extra hundred and then not feel like you're going to burn yourself inside.

CAC: Procedure and Recovery

Participants reported feeling well-informed about the CAC procedure beforehand and about the nature of the process itself. Several participants directly compared and contrasted the two procedures, weighing the different factors they considered to make their decision:

> *And [the doctor] explained to me that, with the VenaSeal, there was less risk with nerve damage and those types of things. So I decided that I liked the idea of the gluing and I booked that through him, had it done.*

> *But basically when I decided on the two, you know, we looked at the literature and the outcomes. And to me, they looked very similar. Pricing was similar. I was not … I would not be happy to have many of the freezing, the needle, so that [laser ablation] really for me was not great, and the potential of discolouration. I'm very fair, I'm a ginger, and I'm pretty sure if I did the lasers I'd have the discolouration of the veins, so [I] decided to go with the glue.*

> *So he explained to me that it [CAC] would be less invasive in that I wouldn't have to have a series of needles to freeze my legs, he wasn't going to have to send something thermal up my legs to burn [the veins], like in the case of laser. He said it was a little lengthier procedure and it takes a little bit of patience on the part of the doctor but, anyway, he gave me lots of information to research on my own around it.*

The CAC procedure itself was a day-procedure, with minimal anesthesia required. Participants reported that, overall, the treatment process was easy to bear, and they expressed their overall satisfaction with it, though some commented about slight sensations of pain or "tugging" during the procedure. Some participants noted feelings of vulnerability during the process due to the nature and location of the treatment.

> *But I tended to call it [a] procedure because I didn't go under, I had a local injection. It wasn't in a hospital. It was in the clinic.*

> *And it was a very good experience. It felt much less intrusive than the ligations I had had a few decades prior.*

> *You could feel tugging, I could feel pressure and I knew things were going on. And again, I think honestly a bigger part of it is just, you're flopped on your belly, your skirt's up to your bum and you feel vulnerable, but again he made me feel comfortable, my husband was there, and there was a lady nurse who made things very comfortable.*

> *The procedure itself is not comfortable but not uncomfortable; it was just weird. And that was very simply done and then the recovery was pretty easy, wearing the [compression] stockings for a week.*

Additionally, the relatively short recovery time after CAC was mentioned as a positive factor in their choice of treatment. Participants reported that they were required to wear compression stockings for a week or so after the procedure, but within a couple of days they were able to resume almost full activities and were back to their normal routine. This was an appealing factor of the CAC procedure, though there were inconveniences in wearing the compression stocking for a week:

> *I put the stocking on. I'm pretty sure I had to have it on for like a week. It was a long time and that was probably the most difficult part of it because it's not very comfortable; your leg is constricted and, you know, sleeping is uncomfortable. And you're just trying to not [hurt the leg] … you don't know what's really there, what's hurt. So I was probably babying it more than I needed to and didn't want to bump it, [saying] "Don't, don't touch it!" to my poor husband in bed and whatever.*

> *Right away I came home, and I'm sure I was putting ice on it regularly ... When I would do school I'd sit down, I put my leg up with ice, but I was making meals and I was making beds and doing laundry right away. It didn't inhibit me from doing life. I just was doing things a little more carefully and trying to keep the little three-year-old away from my leg.*

> *No [restriction on moving after the procedure], not at all. They encouraged movement, so I walked every day. I didn't lift weights, that was the only thing I changed up for a few days. No hard running, so I just laid off for a few days, but in under a week I was back teaching spin and running and lifting weights and there was nothing.*

CAC: Outcomes and Follow-Up

Among people who had a CAC procedure, most reported that its impact was not immediately apparent. It could take from a few days to a few weeks to fully see the decrease in their symptoms, and often any cosmetic improvements were visible much later than the reduction of pain and soreness. However, all participants reported positive outcomes from the procedure and an improvement in their quality of life:

> *It has definitely gotten better. My leg is not perfect, but I'm very happy with the level of care I got and my anxiety is gone about it.*

> *It did take some time to obviously get the blood to move to other places. So there was, you know, a few spicy days, I would call it, when you're working out and it would feel kind of like a zing that you just kind of notice a little bit. Mostly during activities, especially running and spinning, that kind of thing, not walking. But once that got all situated, I actually feel more power in the leg, so more strength, more power, less of that weakness of it giving out, that kind of thing.*

> *But I would say it was … in terms of pain and fatigue and discomfort and sensitivity and just feeling like your heartbeat is in sections of your leg, like it's a gross kind of eerie feeling … and that was almost gone instantaneously for me. Like it worked really well.*

One participant reported a negative experience with CAC, due to an unexpected reaction to a component of the glue used in the procedure. While this participant was initially pleased with the choice of treatment and the ultimate reduction in symptoms, the allergic-type side effect affected their perception of the treatment:

> *In hindsight, I probably would not pick that one again, only because I was allergic to the glue. So I was a very small population that of course reacted to the glue, so it wasn't great.*

The private clinics typically suggested that people return for follow-up and potential sclerotherapy to keep improving the cosmetic appearance of the treated veins. Participants reported being amenable to

this, noting that these follow-up treatments were included in the cost of the procedure, so they would not be any further out-of-pocket:

> *I guess, you know, once you're a client, you're kind of a client for life. So, again, I'm not going into this so my leg can look beautiful like a movie star because I don't ever look that way. But, you know, [the doctor] says if you ever have any problems, then you can come in. So it's kind of a one and done. Like for me, it was really successful, which is great. And the ones, the offshoots are done. If anything does come up over the years, he treats it for free. Which is great.*

> *But you're right in that all these injection treatments are now covered by my initial payment. And my understanding is, if I have any vein issues come back or reoccur, then he covers that as well. So it's a pretty guaranteed treatment.*

BARRIERS TO TREATMENT FOR VARICOSE VEINS

For some participants, the costs of receiving treatment from a private clinic were too high and, faced with this burden, they might delay or avoid treatments altogether. Other participants faced geographical barriers to treatment: some endovenous treatments, including CAC, are mainly done in urban centres in southern Ontario, and even surgical vein stripping could require extensive travel. For participants from northern areas of the province, the lack of local access to various treatment options for varicose veins could be a factor in their decision-making and could become a barrier to successful treatment:

> *I think the other thing would be, it would be a lot easier if we could get that treatment done right [here], so I could go home from the hospital. That is not the case, at least in Thunder Bay.*

> *Somebody else just had, I'm not sure what kind of treatment they had, but I guess you'd call it vein stripping. But that ... involved three trips back to Sioux Lookout for the continuation. I think the first is to tie it off and let it die and then strip it out. I don't know. It was just too tedious, cumbersome, and risk versus reward wasn't there for me to make that decision.*

> *I ended up calling him and, you know, I live in Timmins, Ontario. So it's eight hours from Oakville. So I traveled there, I paid for the procedure. I only have one leg to do.*

Wait times for procedures at private clinics did not seem as burdensome as the costs, participants reported. Typically, they waited a few months to have the procedure done and did not feel that this wait was a barrier to access:

> *It was clear and so I didn't feel like I'm waiting forever for this. It was in a reasonable amount of time.*

> *And then obviously I prompted the next referral, you know, that didn't take too long. And then once I got in with [the doctor] and had my referral, it was, I would say, several months before I had the procedure.*

> *Booking appointments was a challenge just because they are busy. Again, I don't remember a particular issue. Now, I mean, I don't think it happened immediately but I also don't remember it being a concern.*

Several participants commented that they felt that access to varicose vein treatment, including CAC, is limited by a general perception that the treatment is only for cosmetic purposes and is mainly favoured by women. They felt that this has created a stigma around treatment for varicose veins and has led to gender inequality in access to these particular health services:

> *But for me personally, it's tied into my [menstrual] cycle, as I said, so for me I can't help but feel like this is also got some kind of sexism in it, because I really feel like if there were men having to walk around with this level of pain in their leg once a month for five days, you know, I think that this would be probably publicly funded.*
>
> *There's a stigma about it being cosmetic.*
>
> *But I think there's this aspect of sexism that I think my personal experiences that this is part of me, as a female going through this health care system, and that's totally annoying. And then the other thing is, I think there's a perception that varicose veins are an aesthetic thing that somehow this has to do with some optional cosmetic … you're concerned with how your legs look or something. And maybe that's why it's not a priority.*

Discussion

Our engagement with patients on their preferences and values surrounding nonthermal endovenous treatment for varicose veins yielded robust results. All 13 participants spoke extensively about their symptoms and the negative impact of varicose veins on their ability to work, engage in physical activities, and carry out other aspects of daily life.

Additionally, participants had researched and considered a number of treatment options, providing valuable insight into their decision-making around treatment. By discussing their decision-making process, whether in choosing CAC or another treatment option, participants were able to clarify their preferences and values regarding treatment for varicose veins and the potential impact of their decisions. A majority of the participants interviewed had direct lived experience with one nonthermal endovenous procedure (CAC), as well as other treatment options, and were able to provide details of the procedure(s) they received, the recovery process, and the impact of the treatment on their symptoms and quality of life.

We were also able to speak with people about barriers they may have faced in considering and choosing a desired treatment. Participants reported on geographical challenges in accessing different treatment options, as well as financial considerations that may limit their ability to choose an effective treatment. Additionally, some participants felt that gender inequality issues surrounding varicose vein treatments limited their access to a full array of treatment options. This context adds insight into the access to and use of this technology in Ontario.

Conclusions

Varicose veins can cause a number of symptoms, such as pain, aching, swelling, and discolouration, which negatively affect an individual's quality of life. Through interviews, participants reported on these impacts and their health care journey to seek treatment. Participants reported positive impressions of the CAC procedure and its ability to reduce their pain and other symptoms and improve their quality of life.

Conclusions of the Health Technology Assessment

Based on our systematic review of the clinical literature, nonthermal endovenous procedures (mechanochemical ablation [MOCA] and cyanoacrylate adhesive closure [CAC]) for people with symptomatic varicose veins were found to be similarly effective at achieving improvements in clinical symptoms and quality of life compared with thermal endovenous procedures. CAC also led to similar technical outcomes (such as vein closure) compared with thermal endovenous procedures, whereas the technical outcomes after MOCA were poorer than after thermal ablation. In people with active venous ulcers, MOCA led to healing of a greater proportion of ulcers than thermal ablation, similar time to healing, and similar recurrence of venous ulcers. There was very limited evidence comparing CAC with surgical vein stripping; therefore, the evidence remains very uncertain. Complication profiles differed between nonthermal endovenous procedures, thermal ablation, and surgical vein stripping. Major complications were reportedly very rare and minor complications occurred at similar, low frequencies across intervention groups.

Our systematic review of the economic literature identified two European studies that evaluated the cost-effectiveness of nonthermal therapies compared with surgery and thermal therapies, in people with symptomatic varicose veins. Both studies found that thermal ablation procedures were the most cost-effective treatment, although which type of thermal therapy was the optimal strategy depended on the setting and perspective.

Our primary evaluation of cost-effectiveness found that, compared with surgical vein stripping, all nonthermal and thermal endovenous treatments (CAC, MOCA, radiofrequency ablation [RFA], and endovenous laser ablation [EVLA]) were more effective and less costly strategies for treating people with symptomatic varicose veins. The differences in quality-adjusted life-years [QALYs] among endovenous treatments were small, which makes the results very uncertain. If we were to look at the most cost-effective strategy (at a willingness-to-pay value of less than $100,000 per QALY), EVLA is most likely to be cost-effective.

If thermal and nonthermal endovenous treatments are publicly funded in Ontario for adults with symptomatic varicose veins, the potential target population could increase considerably. Assuming an 80% increase in the number of eligible people, we estimate that the annual budget impact would range from $2.59 million in year 1 to $4.35 million in year 5, and that the total 5-year budget impact would be around $17 million.

Among people with varicose veins who we interviewed, nonthermal procedures (specifically CAC) were viewed positively: they reported that this procedure reduced their symptoms and improved quality of life. Participants also reported on geographical challenges in accessing different treatments, as well as financial considerations that may limit their ability to choose an effective treatment option.

Abbreviations

ASVAL	Ambulatory selective varicose vein ablation under local anesthesia (see Glossary)
AVVQ	Aberdeen Varicose Vein Questionnaire
CAC	Cyanoacrylate adhesive closure
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAP	Clinical-Etiology-Anatomy-Pathophysiology classification
CHIVA	Cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire (see Glossary)
CI	Confidence interval
CVI	Chronic venous insufficiency
DVT	Deep vein thrombosis
EVLA	Endovenous laser ablation
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSV	Great saphenous vein
HLS	High ligation and stripping
IQR	Interquartile range
MOCA	Mechanochemical ablation
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
OHIP	Ontario Health Insurance Plan
OHTAC	Ontario Health Technology Advisory Committee
OR	Odds ratio
PROSPERO	International prospective register of systematic reviews
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
SD	Standard deviation
SSV	Small saphenous vein
VCSS	Venous Clinical Severity Scale

Glossary

Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
ASVAL	"Ambulatory selective varicose vein ablation under local anesthesia," ASVAL is a more conservative surgical treatment that aims to preserve the great saphenous vein if possible and removes the side branch veins.
CHIVA	An uncommonly used type of conservative varicose vein surgery that preserves the great saphenous vein and aims to redirect blood flow into the deeper venous system through perforator veins by tying off branch veins, but not ablating or removing them. The procedure is known by the acronym for its French name: cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire (translated roughly as: ambulatory conservative hemodynamic treatment venous insufficiency).
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.
Cost-effectiveness plane	In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Disutility	A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
EuroQol–Five Dimensions (EQ-5D)	The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.
Extended dominance	A health care intervention is considered to be extendedly dominated when it has an incremental cost-effectiveness ratio higher than that of the next most costly or effective comparator. Interventions that are extendedly dominated are ruled out.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Health-related quality of life	Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Incremental net benefit	Incremental net benefit is a summary measure of cost-effectiveness. It incorporates the differences in cost and effect between two health care interventions and the willingness-to-pay value. Net health benefit is calculated as the difference in effect minus the difference in cost divided by the willingness-to-pay value. Net monetary benefit is calculated as the willingness-to-pay value multiplied by the difference in effect minus the difference in cost. An intervention can be considered cost-effective if either the net health or net monetary benefit is greater than zero.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Natural history of a disease	The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.
Neovascularization	After vein removal surgery, the development of new varicose veins either in collateral veins that remain or in new veins that develop at the ligation site. A main cause of recurrent venous insufficiency, symptoms, and retreatment after surgical vein stripping.

Noninferiority trial	A clinical trial designed to test whether a new or experimental treatment is not unacceptably less effective than (not inferior to) another treatment. Noninferiority trials may be used when a new treatment is likely to have a small incremental benefit over an effective control treatment and may have other benefits (e.g., convenience, safety, compliance). A noninferiority trial tests whether the treatment is effective within a predefined, clinically acceptable margin of the control treatment (e.g., are the results similar within 10%).
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Utility	A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Visual analogue scale (VAS)	The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: January 14, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 10, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 02>, Ovid MEDLINE(R) ALL <1946 to January 13, 2020>

Search Strategy:

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1 exp Varicose Veins/ (65299)
2 ((varicose* adj2 vein*) or varicoses or varicosis or varicosit*).ti,ab,kf. (28185)
3 exp Venous Insufficiency/ (17812)
4 (((venous or vein* or valvular) adj2 (insufficien* or incompeten* or reflux)) or venous disease*).ti,ab,kf. (24994)
5 Saphenous Vein/ (28709)
6 (((saphenous or trunk or truncal) adj2 (vein* or insufficien* or reflux or incompeten*)) or GSV or SSV).ti,ab,kf. (36948)
7 ((clinical etiology anatomy pathophysiology or CEAP*) adj2 (C2* or C3* or C4* or C5* or C6*)).ti,ab,kf. (478)
8 lipodermatoscleros*.ti,ab,kf. (717)
9 or/1-8 (137094)
10 exp Cyanoacrylates/ (6513)
11 (cyanoacrylat* or cyano acrylat* or cyanacrylat* or cyanoacrilat* or isobutylcyanoacrylat* or bucr?lat* or cyanobutylacrylat* or butylcyanoacrylat* or polyisobutylcyan?acrylat* or enbucr?lat* or hist?acryl* or ?cyanoacrylat* or CAC).ti,ab,kf. (27106)
12 (venaseal* or venablock* or veclose* or variclose* or sapheon* or vein sealing system*).ti,ab,kf. (157)
13 Ablation Techniques/ (19844)
14 (ablat* adj2 technique*).ti,ab,kf. (7680)
15 (((mechanochemical or mechano chemical) adj3 ablat*) or MOCA).ti,ab,kf. (8880)
16 ((nonthermal or non thermal) adj3 (ablat* or technique* or treatment* or therap*)).ti,ab,kf. (1484)
17 ((nontumescent or non tumescent or tumescentless or NTNT) adj3 (ablat* or technique* or treatment* or therap*)).ti,ab,kf. (108)
18 clarivein*.ti,ab,kf. (114)
19 or/10-18 (65030)
20 9 and 19 (2120)
21 exp Animals/ not Humans/ (16506183)
22 20 not 21 (1249)
23 Case Reports/ (2068890)

24 22 not 23 (1157)
25 limit 24 to english language [Limit not valid in CDSR; records were retained] (1006)
26 limit 25 to yr="2012 -Current" (609)
27 26 use medall,cctr,coch,clhta,cleed (284)
28 varicosis/ (19201)
29 leg varicosis/ (1543)
30 ((varicose* adj2 vein*) or varicoses or varicosis or varicosit*).tw,kw. (27755)
31 vein insufficiency/ (5793)
32 (((venous or vein* or valvular) adj2 (insufficien* or incompeten* or reflux)) or venous disease*).tw,kw. (25565)
33 saphenous vein/ (28709)
34 (((saphenous or trunk or truncal) adj2 (vein* or insufficien* or reflux or incompeten*)) or GSV or SSV).tw,kw. (37106)
35 ((clinical etiology anatomy pathophysiology or CEAP*) adj2 (C2* or C3* or C4* or C5* or C6*)).tw,kw. (482)
36 lipodermatoscleros*.tw,kw. (755)
37 or/28-36 (98831)
38 cyanoacrylate/ (6499)
39 enbucrilate/ (6064)
40 cyanoacrylate derivative/ (1476)
41 bucrilate/ (857)
42 (cyanoacrylat* or cyano acrylat* or cyanacrylat* or cyanoacrilat* or isobutylcyanoacrylat* or bucr?lat* or cyanobutylacrylat* or butylcyanoacrylat* or polyisobutylcyan?acrylat* or enbucr?lat* or hist?acryl* or ?cyanoacrylat* or CAC).tw,kw,dv. (27673)
43 endovenous sealing device/ (43)
44 (venaseal* or venablock* or veclose* or variclose* or sapheon* or vein sealing system*).tw,kw,dv. (186)
45 *ablation therapy/ (4752)
46 (ablat* adj2 technique*).tw,kw,dv. (7950)
47 (((mechanochemical or mechano chemical) adj3 ablat*) or MOCA).tw,kw,dv. (8929)
48 ((nonthermal or non thermal) adj3 (ablat* or technique* or treatment* or therap*)).tw,kw,dv. (1497)
49 ((nontumescent or non tumescent or tumescentless or NTNT) adj3 (ablat* or technique* or treatment* or therap*)).tw,kw,dv. (106)
50 peripheral venous catheter/ (844)
51 clarivein*.tw,kw,dv. (145)
52 or/38-51 (55429)
53 37 and 52 (1323)
54 (exp animal/ or nonhuman/) not exp human/ (10542619)
55 53 not 54 (1308)
56 Case Report/ (4402470)
57 55 not 56 (1101)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (1020)
59 limit 58 to yr="2012 -Current" (853)
60 59 use emez (618)
61 27 or 60 (902)
62 61 use medall (221)
63 61 use emez (618)

64 61 use coch (1)
65 61 use cctr (61)
66 61 use clhta (1)
67 61 use cleed (0)
68 remove duplicates from 61 (662)

Economic Evidence Search

Search date: January 14, 2019

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 10, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 02>, Ovid MEDLINE(R) ALL <1946 to January 13, 2020>

Search Strategy:

---

1 exp Varicose Veins/ (65299)
2 ((varicose* adj2 vein*) or varicoses or varicosis or varicosit*).ti,ab,kf. (28185)
3 exp Venous Insufficiency/ (17812)
4 (((venous or vein* or valvular) adj2 (insufficien* or incompeten* or reflux)) or venous disease*).ti,ab,kf. (24994)
5 Saphenous Vein/ (28709)
6 (((saphenous or trunk or truncal) adj2 (vein* or insufficien* or reflux or incompeten*)) or GSV or SSV).ti,ab,kf. (36948)
7 ((clinical etiology anatomy pathophysiology or CEAP*) adj2 (C2* or C3* or C4* or C5* or C6*)).ti,ab,kf. (478)
8 lipodermatoscleros*.ti,ab,kf. (717)
9 or/1-8 (137094)
10 exp Cyanoacrylates/ (6513)
11 (cyanoacrylat* or cyano acrylat* or cyanacrylat* or cyanoacrilat* or isobutylcyanoacrylat* or bucr?lat* or cyanobutylacrylat* or butylcyanoacrylat* or polyisobutylcyan?acrylat* or enbucr?lat* or hist?acryl* or ?cyanoacrylat* or CAC).ti,ab,kf. (27106)
12 (venaseal* or venablock* or veclose* or variclose* or sapheon* or vein sealing system*).ti,ab,kf. (157)
13 Ablation Techniques/ (19844)
14 (ablat* adj2 technique*).ti,ab,kf. (7680)
15 (((mechanochemical or mechano chemical) adj3 ablat*) or MOCA).ti,ab,kf. (8880)
16 ((nonthermal or non thermal) adj3 (ablat* or technique* or treatment* or therap*)).ti,ab,kf. (1484)
17 ((nontumescent or non tumescent or tumescentless or NTNT) adj3 (ablat* or technique* or treatment* or therap*)).ti,ab,kf. (108)
18 clarivein*.ti,ab,kf. (114)
19 or/10-18 (65030)
20 9 and 19 (2120)

21 exp Animals/ not Humans/ (16506183)
22 20 not 21 (1249)
23 limit 22 to english language [Limit not valid in CDSR; records were retained] (1085)
24 limit 23 to yr="2012 -Current" (653)
25 24 use cleed (0)
26 economics/ (255672)
27 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (854926)
28 economics.fs. (428873)
29 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (922501)
30 exp "costs and cost analysis"/ (593376)
31 (cost or costs or costing or costly).ti. (272653)
32 cost effective*.ti,ab,kf. (339546)
33 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (222986)
34 models, economic/ (13253)
35 markov chains/ or monte carlo method/ (84459)
36 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (44401)
37 (markov or markow or monte carlo).ti,ab,kf. (135158)
38 quality-adjusted life years/ (41742)
39 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (77843)
40 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (127200)
41 or/26-40 (2632134)
42 24 and 41 (62)
43 42 use medall,coch,cctr,clhta (31)
44 25 or 43 (31)
45 varicosis/ (19201)
46 leg varicosis/ (1543)
47 ((varicose* adj2 vein*) or varicoses or varicosis or varicosit*).tw,kw. (27755)
48 vein insufficiency/ (5793)
49 (((venous or vein* or valvular) adj2 (insufficien* or incompeten* or reflux)) or venous disease*).tw,kw. (25565)
50 saphenous vein/ (28709)
51 (((saphenous or trunk or truncal) adj2 (vein* or insufficien* or reflux or incompeten*)) or GSV or SSV).tw,kw. (37106)
52 ((clinical etiology anatomy pathophysiology or CEAP*) adj2 (C2* or C3* or C4* or C5* or C6*)).tw,kw. (482)
53 lipodermatoscleros*.tw,kw. (755)
54 or/45-53 (98831)
55 cyanoacrylate/ (6499)
56 enbucrilate/ (6064)
57 cyanoacrylate derivative/ (1476)
58 bucrilate/ (857)
59 (cyanoacrylat* or cyano acrylat* or cyanacrylat* or cyanoacrilat* or isobutylcyanoacrylat* or bucr?lat* or cyanobutylacrylat* or butylcyanoacrylat* or polyisobutylcyan?acrylat* or enbucr?lat* or hist?acryl* or ?cyanoacrylat* or CAC).tw,kw,dv. (27673)
60 endovenous sealing device/ (43)

61 (venaseal* or venablock* or veclose* or variclose* or sapheon* or vein sealing system*).tw,kw,dv. (186)
62 *ablation therapy/ (4752)
63 (ablat* adj2 technique*).tw,kw,dv. (7950)
64 (((mechanochemical or mechano chemical) adj3 ablat*) or MOCA).tw,kw,dv. (8929)
65 ((nonthermal or non thermal) adj3 (ablat* or technique* or treatment* or therap*)).tw,kw,dv. (1497)
66 ((nontumescent or non tumescent or tumescentless or NTNT) adj3 (ablat* or technique* or treatment* or therap*)).tw,kw,dv. (106)
67 peripheral venous catheter/ (844)
68 clarivein*.tw,kw,dv. (145)
69 or/55-68 (55429)
70 54 and 69 (1323)
71 (exp animal/ or nonhuman/) not exp human/ (10542619)
72 70 not 71 (1308)
73 limit 72 to english language [Limit not valid in CDSR; records were retained] (1204)
74 limit 73 to yr="2012 -Current" (995)
75 Economics/ (255672)
76 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (132695)
77 Economic Aspect/ or exp Economic Evaluation/ (465078)
78 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (948768)
79 exp "Cost"/ (593376)
80 (cost or costs or costing or costly).ti. (272653)
81 cost effective*.tw,kw. (352032)
82 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (234461)
83 Monte Carlo Method/ (67164)
84 (decision adj1 (tree* or analy* or model*)).tw,kw. (48248)
85 (markov or markow or monte carlo).tw,kw. (140243)
86 Quality-Adjusted Life Years/ (41742)
87 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (81730)
88 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (148116)
89 or/75-88 (2258041)
90 74 and 89 (98)
91 90 use emez (66)
92 44 or 91 (97)
93 92 use medall (21)
94 92 use emez (66)
95 92 use coch (1)
96 92 use cctr (8)
97 92 use clhta (1)
98 92 use cleed (0)
99 remove duplicates from 92 (73)

Grey Literature Search

Search dates: January 15–17, 2020

Websites searched:

Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, Italian National Agency for Regional Health Services (AGENAS), Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Ministry of Health Malaysia Health Technology Assessment Section, Swedish Agency for Health Technology Assessment and Assessment of Social Services, PROSPERO, EUnetHTA, ClinicalTrials.gov, Tufts Cost-Effectiveness Analysis Registry

Keywords used:

ablation, endovenous ablation, clarivein, mechanochemical ablation, mechano-chemical ablation, mechanochemical endovenous ablation, MOCA, venaseal, VeClose, venablock, cyanoacrylate, CAC, nonthermal endovenous, nonthermal ablation, non thermal ablation, nontumescent ablation, vein ablation, endovenous mechanical vein, vein sealing, varicose veins, venous insufficiency, varicosis, saphenous, clinical-etiology-anatomy-pathophysiology, CEAP, ablation endoveineuse, varices

Clinical results (included in PRISMA): 21
Economic results (included in PRISMA): 20
Ongoing clinical trials (ClinicalTrials.gov): 13
Ongoing health technology assessments (PROSPERO/EUnetHTA/MSAC): 7

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Randomized Controlled Trials of Mechanochemical Ablation (Cochrane Risk-of-Bias Tool Version 2)

Author, Year	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Mohamed et al, 2020[83]	Low	Low	Low	Low	Low	Low
Vahaaho et al, 2019, 2020[80,85]	Low	Low	Low	Low	Some concerns[b]	Low
Holewijn et al, 2019[79]	Low	Low	Low	Low	Some concerns	Some concerns[c]
Lane et al, 2017[74]	Low	Some concerns	Low	Low	Some concerns	High[d]

[a]Possible risk-of-bias judgments: low, high, or some concerns.
[b]Clinical status outcome poorly described. Appears to be measured by clinical disability scale (CDS) at 1 year whereas the 3-year publication reports Venous Clinical Severity Score (VCSS) (baseline vs. 3 years). Measurement of clinical status, CDS, or VCSS not mentioned in protocol or 1-year publication.
[c]Deviated notably from study protocol: Trial was stopped early due to lack of funding for MOCA and it was determined by the ethical committee to stop. The trial sought to recruit 460 people and follow them for 5 years but enrolled only 213 and followed them for up to 2 years.
[d]The authors did not provide much information about the planned statistical analyses, whether they were intention-to-treat or per protocol, or blinding of outcome assessment, so it was unclear if analyses were appropriate or may have altered results.

Table A2: Risk of Bias[a] Among Randomized Controlled Trials of Cyanoacrylate Adhesive Closure (Cochrane Risk-of-Bias Tool Version 2)

Author, Year	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
VeClose trials[69-72,81]	Low	Low	Low	Low	Low	Low
Eroglu and Yasim, 2018[65]	Low	Some concerns[b]	Low	Low	Low	Some concerns[b]

[a]Possible risk of bias judgments: low, high, or some concerns.
[b]3–10 people per group did not receive intended intervention for either "no particular reason" or "unhappy with assigned treatment."

Table A3: Risk of Bias[a] Among Nonrandomized Studies for the Comparison of Mechanochemical Ablation and Endovenous Laser Ablation or Radiofrequency Ablation

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure (Intervention)	Blinding of Outcome Assessments	Incomplete Outcome data	Selective Outcome Reporting
Kim et al, 2019[78]	Low	Low	Low	Low	Low	Low
Moon et al, 2017[77]	Low	Unclear[b]	Low	Low	Low	Low
Vun et al, 2015[76]	Low	Unclear[c]	Low	Low	High[d]	Low
van Eekeren et al, 2013[75]	Low	Low	Low	Unclear[e]	Low	Low

Abbreviations: EVLA, endovenous laser ablation; RFA, radiofrequency ablation; RoBANS, Risk of Bias Assessment tool for Nonrandomized Studies.

[a]Risk of bias assessed using RoBANS.[50] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b]Confounders (measurement of or adjustment for) were not mentioned in design or analysis.

[c]No information about consideration of and use of confounders in analysis.

[d]Lack of full data reported on outcomes in vein closure for RFA and EVLA; only one citation to refer to both.

[e]No blinding of outcome assessment, and outcomes were assessed by both objective and standardized self-report tools from patients. Not clear if this affected outcome measurement.

Table A4: Risk of Bias[a] Among Nonrandomized Studies for the Comparison of Cyanoacrylate Adhesive Closure and Endovenous Laser Ablation, Radiofrequency Ablation, or Surgical Vein Stripping

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure (Intervention)	Blinding of Outcome Assessments	Incomplete Outcome data	Selective Outcome Reporting
Ay et al 2020[92]	Low	Unclear[b]	Low	Unclear[c]	Low	High[d]
Kubat et al, 2020[82]	Low	Low	Low	Unclear[c]	Low	Unclear[e]
Kubat et al, 2019[62]	Low	Low	Low	Unclear[c]	Low	Low
McGuiness et al, 2019[67]	Low	Low	Low	Low	Unclear[f]	Low
Ovali and Sevin, 2019[66]	Low	Low	Low	Unclear[c]	Unclear[f]	Low
Yang et al, 2019[63]	Low	Unclear[b]	Low	Low	High[g]	Low
Bademci et al, 2019[64]	Low	Low	Low	Unclear[c]	Low	Low
Koramaz et al, 2017[68]	High[h]	Low	Low	Unclear[c]	Low	Low
Bozkurt and Yilmaz, 2016[48]	Low	Low	Low	Low	Unclear[d]	Low

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; RFA, radiofrequency ablation; RoBANS, Risk of Bias Assessment tool for Nonrandomized Studies.

[a]Risk of bias assessed using RoBANS.[50] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b]No information about measurement or accounting for any confounders in design or analysis.

[c]No blinding of outcome assessment, and outcomes were assessed by both objective and standardized self-report tools from patients. Not clear if this affected outcome measurement.

[d]No protocol. Primary outcomes not described clearly; analysis included high ligation and stripping in vein closure analysis, and the paper also describes "satisfaction" throughout results and discussion but is not pre-specified in methods as an outcome.

[e]Success (total vein occlusion) is described in methods, but not in results. However, recurrence is defined as corollary to success and reported in detail as primary outcome.

[f]Total number of participants enrolled and treated is greater than the number with outcomes assessed; similar for both groups, but reasons for the missing data are unclear.

[g]Denominators for vein segments treated differs substantively between baseline characteristics (Table 1 in the publication) and results (Table 2), and to a greater extent for RFA group.

[h]CAC group differs from the EVLA group with respect to study period, as participants were selected from 2 different time periods.

Table A5: GRADE Evidence Profile for Mechanochemical Ablation Compared With Endovenous Laser Ablation for Chronic Venous Insufficiency

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Vein Closure							
2 (RCTs)[74,80,83]	No serious limitations[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[c]	None detected	None	⨁⨁⨁ Moderate
1 (NRS)[76]	Serious limitations (−1)[d]	None[e]	No serious limitations	No serious limitations	None detected	None	⨁ Very low
Recanalization							
2 (RCTs)[80,83]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[f]	None detected	None	⨁⨁⨁ Moderate
1 (NRS)[76]	Serious limitations (−1)[d]	None[e]	No serious limitations	No serious limitations	None detected	None	⨁ Very low
Clinical Symptom Improvement							
2 (RCTs)[83,85]	Serious limitations (−1)	None[e]	No serious limitations	No serious limitations	None detected	None	⨁⨁⨁ Moderate
Quality of Life Improvement							
2 (RCTs)[80,83]	No serious limitations	Serious limitations (−1)[g]	No serious limitations	No serious limitations	None detected	None	⨁⨁⨁⨁ High
Patient Satisfaction							
1 (RCT)[83]	No serious limitations	None[e]	No serious limitations	No serious limitations	None detected	None	⨁⨁⨁⨁ High
Recovery Time							
2 (RCTs)[80,83]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	None detected	None	⨁⨁⨁ Moderate

Abbreviations: EVLA, endovenous laser ablation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MOCA, mechanochemical ablation; NRS, nonrandomized study; RCT, randomized controlled trial.

[a]2 studies were judged to be at low risk of bias overall while one (Lane et al, 2017[72]) was judged to be at high risk of bias overall (Table A1).

[b]All point estimates favour EVLA by approximately 10%–15% except Lane et al, 2017,[72] at 1-month follow-up only, which is captured in downgrade for imprecision.

Notes continued next page.

Table A5 notes, continued:

[c]Meta-analysis estimate favours EVLA clearly, but the confidence intervals are wide (~20 points). One effect estimate favours MOCA, another favours EVLA but the confidence interval crosses the null.

[d]Judged unclear on 1 domain and high on another (see our Table A3).

[e]Not evaluable because of a single study.

[f]Wide confidence intervals but same direction/clinical action for both upper and lower bound.

[g]Notably different baseline and post-treatment scores in each of the studies.[80,83]

Table A6: GRADE Evidence Profile for Mechanochemical Ablation Compared With Radiofrequency Ablation for Chronic Venous Insufficiency

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Vein Closure							
3 (RCTs)[79,80]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations[b]	Undetected	None	⨁⨁⨁ Moderate
1 (NRS)[76]	Serious limitations (−1)[c]	None[d]	No serious limitations	No serious limitations	None detected	None	⨁ Very low
Recanalization							
2 (RCTs)[79,80]	Serious limitations (−1)[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
1 (NRS)[76]	Serious limitations (−1)[c]	None[d]	No serious limitations	No serious limitations	None detected	None	⨁ Very low
Clinical Symptom Improvement							
3 (RCTs)[74,79,85]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
1 (NRS)[75]	No serious limitations	None[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Quality of Life Improvement							
3 (RCTs)[74,79,80]	Serious limitations (−1)[a]	Serious limitations (−1)[f]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 (NRS)[75]	No serious limitations	None[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Patient Satisfaction							
1 (RCT)[79]	Serious limitations (−1)[a]	None[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
Recovery Time							
3 (RCTs)[74,79,80]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[g]	Undetected	None	⨁⨁ Low
1 (NRS)[75]	No serious limitations	None[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MOCA, mechanochemical ablation; NRS, nonrandomized study; RCT, randomized controlled trial.

[a]Vahaaho et al, 2019[78] had low risk of bias but Holewijn et al, 2019[77] had some concerns mainly around huge deviation from protocol (lost funding for MOCA) and Lane et al, 2017[72] was judged to be at high risk of bias overall; see Table A1.

[b]All in same direction, confidence intervals are ~10 points wide; only 1 confidence interval touches 1 but does not cross (Holewijn et al, 2019[77] at 24 month follow-up).

[c]Rated as unclear risk of bias on confounding variables and high risk of bias on incomplete outcome data (see Table A3 for risk of bias assessment).

[d]Not evaluable because of a single study.

[e]Holewijn et al, 2019[77]: issues with risk of bias overall due to protocol deviations; Lane et al, 2017[72]: high risk of bias overall with some concerns (see Table A1).

[f]Very different quality-of-life baseline and post-treatment scores in the studies: in Holewijn et al, 2019[77] baseline was ~13, post-treatment 4–7; Vahaaho et al, 2019[78] started at ~16, post-treatment ~5–6; in Lane et al, 2017[72] scores were high at baseline (almost 20) and 13 after treatment.

[g]Lane et al, 2017[72] reported wider interquartile range than other studies, and almost double the number of days recovering, so we are uncertain about true effect.

Table A7: GRADE Evidence Profile for Cyanoacrylate Adhesive Closure Compared With Radiofrequency Ablation for Chronic Venous Insufficiency

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Vein Closure							
2 (RCTs)[65,81]	No serious limitations	No serious limitations[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕⊕ Moderate
4 (NRS)[63,64,66,92]	Serious limitations (–1)	No serious limitations[a]	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Recanalization							
2 (RCTs)[65,81]	No serious limitations	No serious limitations[c]	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕⊕ Moderate
4 (NRS)[63,64,66,92]	Serious limitations (–1)	No serious limitations[c]	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Clinical Symptom Improvement							
2 (RCTs)[65,81]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕⊕ Moderate
3 (NRS)[64,66,92]	Serious limitations (–1)	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Quality of Life Improvement							
1 (RCT, VeClose trial)[81]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕⊕ Moderate
3 (NRS)[64,66,92]	No serious limitations	No serious limitations[d]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Patient Satisfaction							
1 (RCT)[81]	Serious limitations (−1)[e]	None[f]	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Recovery Time							
1 (RCT)[65]	Serious limitations (−1)[g]	None[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomised studies; RCT, randomized controlled trial.

[a]All estimates had same direction, similar magnitude with 1 exception (see our Figure 6).

[b]Determined noninferior with 10% noninferiority margin at all time points, 3 days to 60 months post-treatment; however, likely lacking power due to loss to follow-up at later timepoints (VeClose trial).

[c]Almost all estimates had same direction, similar magnitude (see our Figures 8a and 8b).

[d]Effect was consistent across 3 larger studies, and the fourth small study, which had limitations, found the opposite effect.

[e]Most information for this outcome comes from publications with longer-term follow-up results of VeClose trial; these involved much smaller numbers and results may be biased given recovery time is a subjective outcome.

[f]Not evaluable because of a single study.

[g]Some concerns with risk of bias, see our table A2 for full details.

Table A8: GRADE Evidence Profile for Cyanoacrylate Adhesive Closure Compared With Endovenous Laser Ablation for Chronic Venous Insufficiency

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Vein Closure							
1(RCT)[65]	No serious limitations	None[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁⨁ Moderate
3 (NRS)[48,67,68]	Some serious limitations (−1)[c]	No serious limitations[d]	No serious limitations	Some serious limitations (−1)[e]	Undetected	None	⨁ Very low
Recanalization							
1(RCT)[65]	No serious limitations	None[a]	No serious limitations	Serious limitations (−1)[f]	Undetected	None	⨁⨁⨁ Moderate
3 (NRS)[48,67,68]	Some serious limitations (−1)[c]	No serious limitations[d]	No serious limitations	Some serious limitations (−1)[e]	Undetected	None	⨁ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Clinical Symptom Improvement							
1(RCT)[65]	No serious limitations	None[a]	No serious limitations	Serious limitations (−1)[f]	Undetected	None	⊕⊕⊕ Moderate
2 (NRS)[48,68]	Some serious limitations (−1)[g]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Quality of Life Improvement							
1 (NRS)[48]	No serious limitations	None[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Patient Satisfaction							
1 (RCT)[65]	Serious limitations (−1)[h]	None[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Recovery Time							
1 (RCT)[65]	Serious limitations (−1)[h]	None[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: CAC, cyanoacrylate adhesive closure; EVLA, endovenous laser ablation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomized study; RCT, randomized controlled trial; RFA, radiofrequency ablation.

[a]Not evaluable because of a single study.

[b]Power suspected to be compromised due to loss to follow-up in all arms, especially thermal ablation (CAC 4%; EVLA 21%; RFA 15%).

[c]1 study (Koramaz et al, 2017[66]) high on participant selection; 2 studies (McGuinness et al, 2019[65] and Boskurt and Yilmaz, 2016[46]) unclear on incomplete outcome data (see Table A4).

[d]All but McGuinness et al, 2019[65] favoured CAC; McGuinness et al did not specify a discrete follow-up time so unclear if it is inconsistent.

[e]Confidence intervals of 3 estimates (including the summary estimate from our meta-analysis) cross null.

[f]Low event rate and relatively small sample size (175 per group), optimal information size was not met.

[g]1 study (Koramaz et al, 2017[66]) high on participant selection.

[h]Some concerns with risk of bias for this study. See our table A2 for full assessment.

Table A9: GRADE Evidence Profile for Cyanoacrylate Adhesive Closure Compared With Radiofrequency Ablation, Endovenous Laser Ablation, or Surgical Vein Stripping for Great Saphenous Vein Insufficiency With Vein Diameter ≥ 10 mm

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Vein Closure							
1 (NRS)[62]	No serious limitations	None[a]	Serious limitations (−1)[b]	No serious limitations	Undetected	None	⨁ Very low
Recanalization							
1 (NRS)[62]	No serious limitations	None[a]	Serious limitations (−1)[b]	No serious limitations	Undetected	None	⨁ Very low
Clinical Symptom Improvement							
1 (NRS)[62]	No serious limitations	None[a]	Serious limitations (−1)[b]	No serious limitations	Undetected	None	⨁ Very low

Abbreviations: CVI, chronic venous insufficiency; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomized study.

[a]Not evaluable because of a single study.

[b]Eligibility criteria for this study were restricted to vein diameter ≥ 10 mm which is a subset of the CVI population. However, all treatments studied are options for all patients with CVI.

Table A10: GRADE Evidence Profile for Cyanoacrylate Adhesive Closure Compared With Surgical Vein Stripping

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Clinical Symptoms							
1 (NRS)[92]	Serious limitations (–1)[a]	None[b]	Serious limitations (–1)[c]	No serious limitations	Undetected	None	⨁ Very low
Quality of Life							
1 (NRS)[92]	Serious limitations (–1)[a]	None[b]	Serious limitations (–1)	No serious limitations	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomized study.

[a]Assessed as high or unclear risk of bias on several dimensions of potential bias; see our Table A4 for details.

[b]Not evaluable because of a single study.

[c]Study participants were a bit younger on average than all other studies (see our Table 15) and may not represent the full spectrum of patients seen in Ontario.

Table A11: GRADE Evidence Profile for Cyanoacrylate Adhesive Closure Compared With Radiofrequency Ablation, Endovenous Laser Ablation, or Surgical Vein Stripping for Small Saphenous Venous Insufficiency

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Recurrence							
1 (NRS)[82]	No serious limitations[a]	None[b]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Clinical Symptoms							
1 (NRS)[82]	No serious limitations[a]	None[b]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomized study.

[a]Risk of bias judged to be unclear for blinding of outcome assessment, and incomplete outcome reporting judged to not likely influence assessment of this outcome.

[b]Not evaluable because of a single study.

Table A12: GRADE Evidence Profile for Mechanochemical Ablation Compared With Thermal Ablation for C6 Severity Venous Disease

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Ulcer Healing							
1 (NRS)[78]	No serious limitations[a]	None[b]	No serious limitations	No serious limitations[c]	Undetected	None	⨁⨁ Low
Time to Ulcer Healing							
1 (NRS)[78]	No serious limitations[a]	None[b]	No serious limitations	No serious limitations[c]	Undetected	None	⨁⨁ Low
Venous Ulcer Recurrence							
1 (NRS)[78]	No serious limitations[a]	None[b]	No serious limitations	No serious limitations[c]	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NRS, nonrandomized study.

[a]Assessed as low risk of bias; see our Table A3 for details.

[b]Not evaluable because of a single study.

[c]The study has small sample size and uneven group sizes. However, considering that the effects observed for binary outcomes were quite large (ulcer healing, time to healing) as well as for recurrence, the result yields similar clinical recommendations. Thus, we did not rate down for imprecision nor rate up for large effect.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Gohel MS, Heatley F, Liu X, et al. A randomized trial of early endovenous ablation in venous ulceration. N Engl J Med. 2018;378(22):2105–2114. doi:10.1056/NEJMoa1801214	Not comparison of interest
Kolluri R, Gibson K, Cher D, Madsen M, Weiss R, Morrison N. Roll-in phase analysis of clinical study of cyanoacrylate closure for incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord. 2016;4(4):407–415. doi:10.1016/j.jvsv.2016.06.017	Not comparison of interest
Tang TY, Yap CJQ, Chan SL, et al. Early results (3 months) of an Asian prospective multicenter VenaSeal real-world postmarket evaluation to investigate the efficacy and safety of cyanoacrylate endovenous ablation for varicose veins. J Vasc Surg Venous Lymphatic Disord. 2020; no pagination. doi:10.1016/j.jvsv.2020.03.020	Noncomparative study

Appendix 4: Clinical Review, Additional Tables and Figures

Table A13: Characteristics of Identified Systematic Reviews

Author, Year	Literature Search Dates	Databases Searched	Analysis Type (Eligible Studies)	Relevant Interventions	Outcomes
Dimech and Cassar, 2020[60]	Inception – Oct 2018	PubMed, Embase, Scopus, Cochrane Library, Science Direct	Narrative (RCT, NRS, case series)	CAC, EVLA, RFA	Vein closure, clinical class, HRQOL, phlebitis, complications
Nugroho et al, 2020[59]	Inception – Jul 2019	PubMed, Cochrane Library	MA (RCT)	MOCA, RFA, EVLA	Vein closure, complications, AEs
Kolluri et al, 2020[61]	Jan 1996 – Sep 2018	PubMed, Embase, Cochrane Library, Google Scholar, Clinical Trials Registry	NMA (RCT)	MOCA, CAC, RFA, EVLA, surgery	Vein closure, clinical symptoms, QOL, HRQOL, post-operative pain
Garcia-Carpintero et al, 2020[54]	Inception – Sep 2018	PubMed, Embase, Web of Science, Scopus, Cochrane Library, CRD	MA (RCT, NRS, case series)	CAC, RFA, EVLA	Vein closure, clinical symptoms, HRQOL, AEs, recovery time, return to work
Hassanin et al, 2019[10]	Inception – Jan 2019	MEDLINE, Embase, CINAHL, Cochrane Library	MA (RCT, NRS)	Nonthermal (CAC, MOCA), thermal (RFA, EVLA)	Vein closure, clinical symptoms, HRQOL, procedural pain, complications
Harlock et al, 2018[56]	Inception – Jan 2017	MEDLINE, Embase, Cochrane Central	MA (RCT, quasi-RCT)	Nontumescent (CAC, MOCA), tumescent (RFA)	Clinical symptoms, HRQOL, ablation failure, procedural pain
Epstein et al, 2018[13]	1974 – Jan 2017	MEDLINE	NMA (RCT)	CAC, MOCA, RFA, EVLA, UGFS	QOL, reintervention, time off work
Sun et al, 2017[52]	Inception – Mar 2017	MEDLINE, Embase, Cochrane Central	MA (RCT, NRS)	MOCA, RFA	Vein closure, clinical symptoms, QOL, HRQOL, absence of technical failure, pain, return to work/activity

Author, Year	Literature Search Dates	Databases Searched	Analysis Type (Eligible Studies)	Relevant Interventions	Outcomes
Witte et al, 2017[53]	Inception – Oct 2016	PubMed, Embase, Cochrane Library	Narrative (RCT, NRS)	MOCA, RFA	Vein closure, clinical symptoms, HRQOL, technical success, major complications
Kugler and Brown, 2017[58]	Jan 2000 – Aug 2016	MEDLINE	Narrative (prospective studies, literature reviews)	MOCA, sclerotherapy, RFA	Vein closure, clinical symptoms,[a] pain, recovery,[a] complications[a]
Hirsch, 2017[57]	Inception – Jul 2016	PubMed	Narrative (NR)	CAC, RFA	Vein closure,[a] clinical symptoms,[a] neurological side effects[a]
Vos et al, 2016[55]	Jan 1966 – Dec 2016	MEDLINE, Embase, CINAHL, Cochrane Library	MA (RCT, prospective NRS)	CAC, MOCA, RFA	Vein closure, clinical symptoms,[a] HRQOL,[a] complications[a]

Abbreviations: AE, adverse event; CAC, cyanoacrylate adhesive closure; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CRD, Centre for Reviews and Dissemination; EVLA, endovenous laser ablation; HRQOL, health-related quality of life; MA, meta-analysis; MOCA, mechanochemical ablation; NMA, network meta-analysis; NR, not reported; NRS, nonrandomized study; QOL, quality of life; RFA, radiofrequency ablation; UGFS, ultrasound guided foam sclerotherapy.

[a]Outcome reported for only some comparisons or interventions.

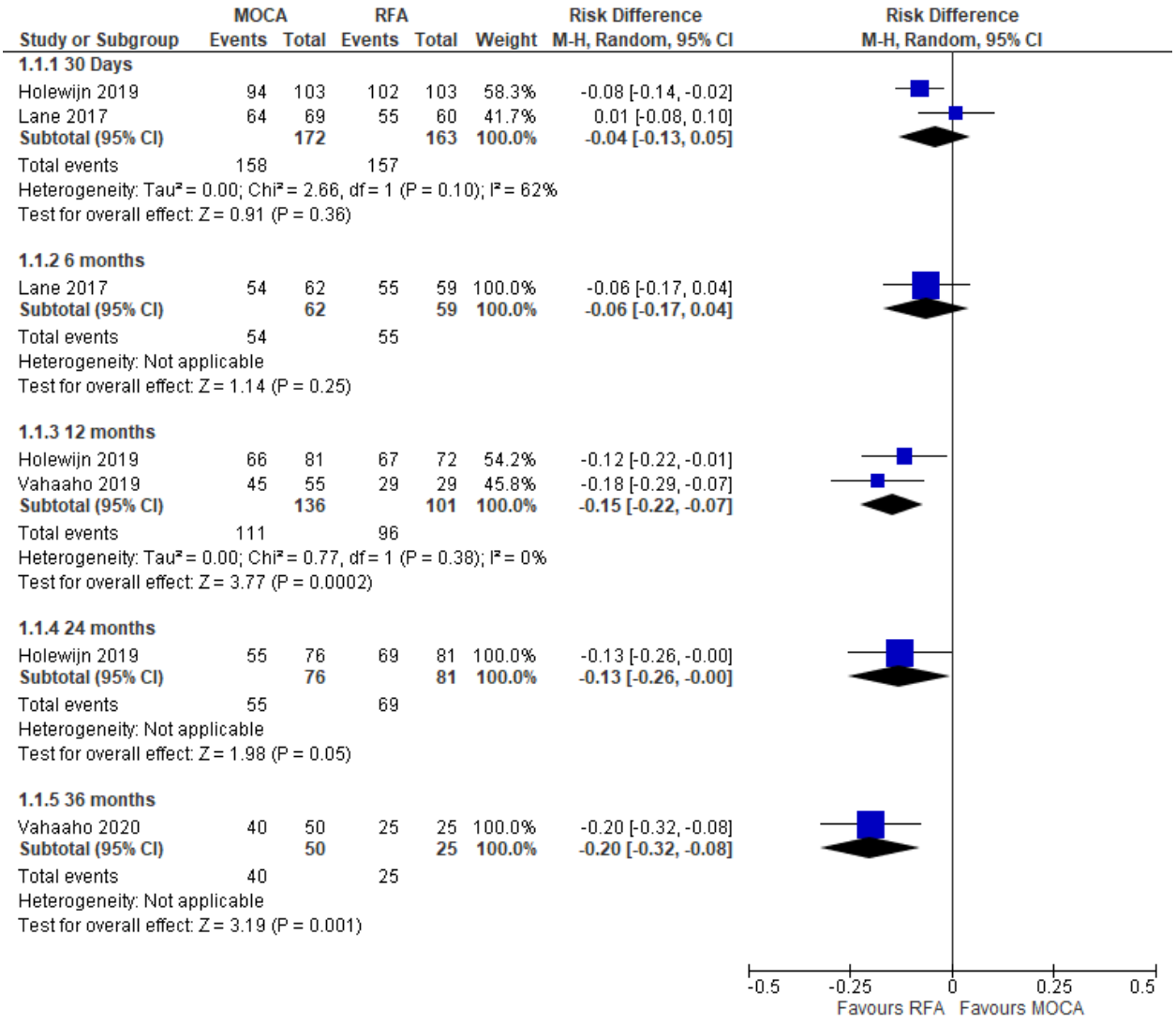

Figure A1: Risk Difference for Vein Closure in Randomized Controlled Trials Comparing Mechanochemical Ablation and Radiofrequency Ablation

Abbreviations: CI, confidence interval; Mantel-Haenszel; MOCA, mechanochemical ablation; RFA, radiofrequency ablation. Event is total vein closure, except for Lane et al,[74] which includes both complete and proximal vein closure only (see footnote c in Table 4). A random effects model was used in our meta-analysis because the distribution of venous disease severity differed between the populations in the studies by Holewijn et al[79] and Vahaaho et al, 2019.[80] However, this was not considered to be clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Lane et al, 2017[74]; Holewijn et al, 2019[79]; Vahaaho et al, 2019,[80] 2020.[85]

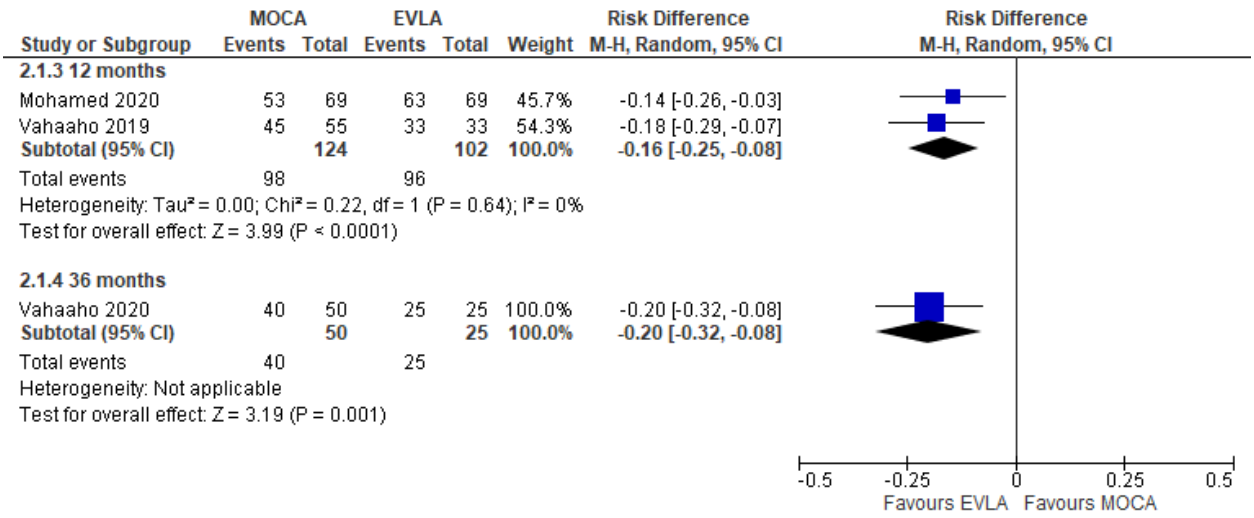

Figure A2: Risk Difference for Vein Closure in Randomized Controlled Trials Comparing Mechanochemical Ablation and Endovenous Laser Ablation

Abbreviations: CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel; MOCA, mechanochemical ablation.

Event is total vein closure. A random effects model was used in our meta-analysis because the distribution of venous disease severity differed between the trials by Mohamed et al[83] and Vahaaho et al, 2019.[80] However, this was not considered as clinically meaningful heterogeneity for this outcome, so the data were pooled.

Data sources: Mohamed et al, 2020[83]; Vahaaho et al, 2019.[80]

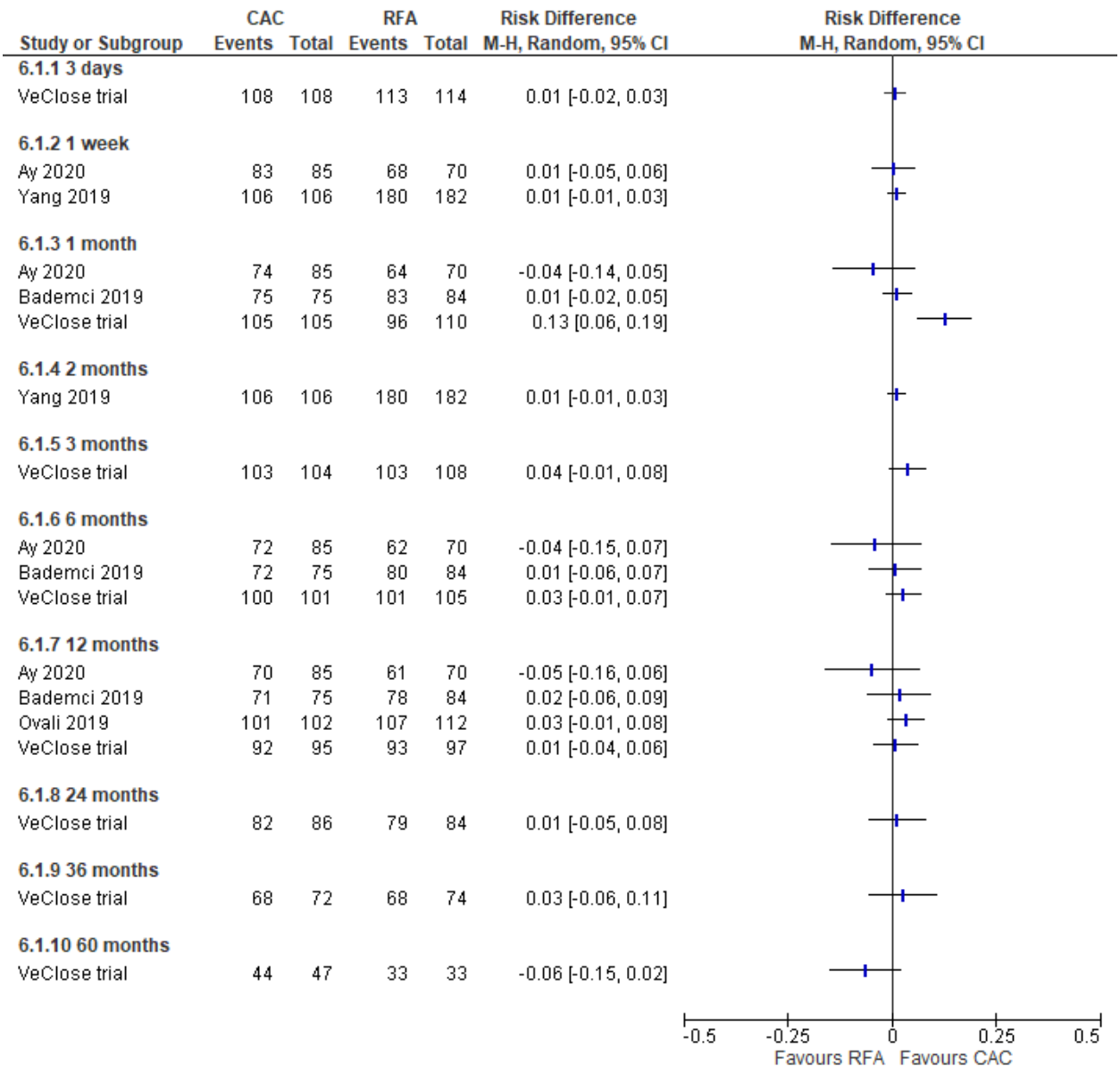

Figure A3: Risk Difference for Vein Closure in Studies Comparing Cyanoacrylate Adhesive Closure and Radiofrequency Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; M-H, Mantel-Haenszel; RFA, radiofrequency ablation.

Data from both randomized controlled trials and nonrandomized studies. Estimates not pooled due to presence of methodological diversity in addition to either statistical heterogeneity (6-month data) or clinical diversity (1-month, 6-month, and 12-month data).

Data sources: Ay et al, 2020[92]; Bademci et al, 2019[64]; Ovali and Sevin, 2019[66]; VeClose trial 2015-2020[69-72,81]; Yang et al, 2019.[63]

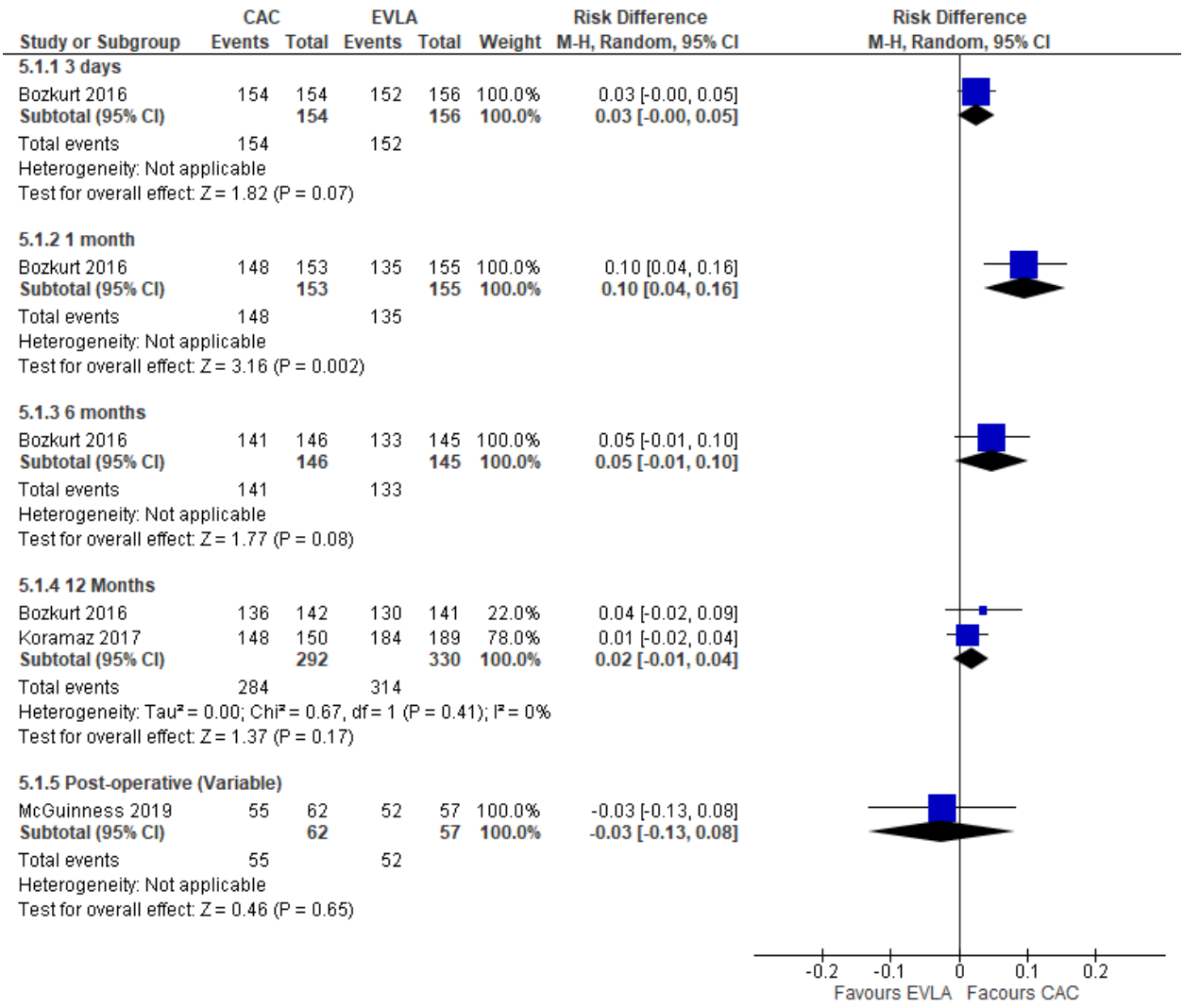

Figure A4: Risk Difference for Vein Closure in Studies Comparing Cyanoacrylate Adhesive Closure and Endovenous Laser Ablation

Abbreviations: CAC, cyanoacrylate adhesive closure; CI, confidence interval; EVLA, endovenous laser ablation; M-H, Mantel-Haenszel.

Events are instances of complete vein closure. Statistical heterogeneity was not an issue; however, a random effects model was used in our meta-analysis to account for differences between disease severity in the studies by Bozkurt and Yilmaz[48] and Koramaz et al.[68]

Data sources: Bozkurt and Yilmaz, 2016[48]; Koramaz et al, 2017[68]; McGuinness et al, 2019.[67]

Appendix 5: Results of Applicability Checklist for Studies Included in the Economic Literature Review

Table A14: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Nonthermal Endovenous Treatments for Varicose Veins

Author, Year, Country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Epstein et al, 2018,[13] Spain/UK	Yes	Yes	No	Yes, UK National Health Service and social care system	Yes	Yes, 3.5% annually	Yes	Partially	Partially applicable
Inderhaug et al, 2018,[95] Norway	Yes	Yes	No	Yes, societal and health care payer in Norwegian setting	Yes	NA (time horizon of 1 year)	Yes	Yes	Partially applicable

Abbreviations: NA, not applicable; UK, United Kingdom.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 6: Budget Impact Analysis, Additional Results

Table A15: Budget Impact Analysis, Reference Case Results by Cost Category

	Total Costs and Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current Scenario						
Total cost	**6.43**	**6.43**	**6.43**	**6.43**	**6.43**	**32.17**
Health care[b]	4.82	4.82	4.82	4.82	4.82	24.12
Devices for endovenous treatment[c]	0	0	0	0	0	0
Overhead	1.61	1.61	1.61	1.61	1.61	8.05
New Scenario						
Total cost	**9.02**	**9.38**	**9.70**	**10.24**	**10.78**	**49.13**
Health care[b]	4.01	3.70	3.32	3.50	3.69	18.21
Devices for endovenous treatment[c]	3.11	3.76	4.47	4.71	4.96	21.02
Overhead	1.90	1.92	1.92	2.03	2.13	9.89
Budget Impact						
Total budget impact	**2.59**	**2.94**	**3.27**	**3.81**	**4.35**	**16.96**
Health care[b]	−0.82	−1.13	−1.51	−1.32	−1.14	−5.91
Devices for endovenous treatment[c]	3.11	3.76	4.47	4.71	4.96	21.02
Overhead	0.29	0.31	0.31	0.42	0.52	1.84

Note: Some numbers may appear inexact due to rounding. Negative costs indicate savings.

[a]All costs are in 2020 Canadian dollars.

[b]Direct health care cost, such as hospital costs (operating room, recovery room, etc.) and professional fees.

[c]Costs for device kit, disposable materials, and equipment and maintenance.

Appendix 7: Letter of Information

Ontario Health

LETTER OF INFORMATION

Ontario Health is conducting a review of **nonthermal treatments for varicose veins**. The purpose is to understand whether this treatment should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and family members of those who may have experience with varicose veins and nonthermal treatments, or who may have attempted to access it. Our goal is always to make sure the lived-experience of individuals and families are considered in the funding recommendations for this test.

WHAT DO YOU NEED FROM PARTICIPANTS?

- ✓ 20-30 minutes of time for a phone or in-person interview to hear about their experiences
- ✓ Permission to audio- (not video-) record the interview

WHAT PARTICIPATION INVOLVES

If a participant agrees to share their experiences, they will be asked to have an interview with Ontario Health staff. The interview will likely last 20-30 minutes. It will be held in a private location or over the telephone. With consent, the interview will be audio-recorded. The interviewer will ask questions about perspectives of varicose veins, decision-making and more general thoughts about nonthermal treatments and the use of these treatments in Ontario.

Participation is voluntary. Those who volunteer may decide not to participate, refuse to answer any questions or withdraw before the interview. Withdrawal will in no way affect the care received.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from the interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, participants can speak to our staff.

If you have any questions, please contact Ontario Health staff:

Appendix 8: Interview Guide

Interview for nonthermal treatment of varicose veins HTA

Intro
Explain Ontario Health purpose, HTA process, and purpose of interview

Lived Experience
Development of symptoms – both physical and sensory
Impact of symptoms on quality of life
Medical journey to receiving diagnosis and subsequent therapies

Treatments for Varicose Veins
Decision-making surrounding different treatment options – what factors were important/influential in making decision?
Information about different treatments – readily available?
Access to treatments; any barriers that existed?

Nonthermal Treatment (CAC)
Information about CAC (if applicable)
Decision-making around undergoing CAC (if applicable)
Procedure itself and impact of CAC; quality of life, side effects, etc.

Overall thoughts on the use of CAC and its potential impact?

Abbreviations: CAC, cyanoacrylate adhesive closure; HTA, health technology assessment.

References

(1) Vascular Disease Foundation. Chronic venous insufficiency [Internet]. Vienna (VA): The Foundation; 2012 [cited 2019 Nov 1]. Available from: http://vasculardisease.org/flyers/chronic-venous-insufficiency-flyer.pdf

(2) Vascular Disease Foundation. Focus on varicose veins [Internet]. Vienna (VA): The Foundation; 2012 [cited 2019 Nov 1]. Available from: http://vasculardisease.org/flyers/focus-on-varicose-veins-flyer.pdf

(3) Piazza G. Varicose veins. Circulation. 2014;130(7):582-7.

(4) Carandina S, Mari C, De Palma M, Marcellino MG, Cisno C, Legnaro A, et al. Varicose vein stripping vs haemodynamic correction (CHIVA): a long term randomised trial. Eur J Vasc Endovasc Surg. 2008;35(2):230-7.

(5) National Institute for Health and Care Excellence. Varicose veins: diagnosis and management (CG168) [Internet]. London (UK): The Institute; 2013 [cited 2019 Nov 5]. Available from: https://www.nice.org.uk/guidance/cg168

(6) Meissner MH, Gloviczki P, Bergan J, Kistner RL, Morrison N, Pannier F, et al. Primary chronic venous disorders. J Vasc Surg. 2007;46 Suppl S:54S-67S.

(7) Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004;40(6):1248-52.

(8) Wrona M, Jockel KH, Pannier F, Bock E, Hoffmann B, Rabe E. Association of venous disorders with leg symptoms: results from the Bonn Vein Study 1. Eur J Vasc Endovasc Surg. 2015;50(3):360-7.

(9) Jull A, Muchoney S, Parag V, Wadham A, Bullen C, Waters J. Impact of venous leg ulceration on health-related quality of life: a synthesis of data from randomized controlled trials compared to population norms. Wound Repair Regen. 2018;26(2):206-12.

(10) Hassanin A, Aherne TM, Greene G, Boyle E, Egan B, Tierney S, et al. A systematic review and meta-analysis of comparative studies comparing nonthermal versus thermal endovenous ablation in superficial venous incompetence. J Vasc Surg Venous Lymphat Disord. 2019;7(6):902-13 e3.

(11) National Institute for Health and Care Excellence. Endovenous mechanochemical ablation for varicose veins (IPG 557) [Internet]. London (UK): The Institute; 2016 [cited 2019 Nov 8]. Available from: https://www.nice.org.uk/guidance/ipg557

(12) Adhikari A, Criqui MH, V W, Denenberg JO, Fronek A, Langer RD, et al. The epidemiology of chronic venous diseases. Phlebology. 2000;15(1):2-8.

(13) Epstein D, Onida S, Bootun R, Ortega-Ortega M, Davies AH. Cost-effectiveness of current and emerging treatments of varicose veins. Value Health. 2018;21(8):911-20.

(14) Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. Am J Prev Med. 1988;4(2):96-101.

(15) Jawien A, Grzela T, Ochwat A. Prevalence of chronic venous insufficiency in men and women in Poland: multicenter cross-sectional study in 40095 patients. Phlebology. 2003;18:110-21.

(16) Kurz X, Lamping DL, Kahn SR, Baccaglini U, Zuccarelli F, Spreafico G, et al. Do varicose veins affect quality of life? Results of an international population-based study. J Vasc Surg. 2001;34(4):641-8.

(17) Medical Advisory Secretariat. Endovascular radiofrequency ablation for varicose veins: an evidence-based analysis. Ont Health Technol Assess Ser. 2011;11(1):1-93.

(18) Health Quality Ontario. Quality standards. Venous leg ulcers: care for patients in all settings [Internet]. Toronto (ON): Queen's Printer for Ontario; 2017 [cited 2019 Nov]. Available from:

https://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-venous-leg-ulcers-clinical-guide-en.pdf

(19) Health Quality Ontario. Compression stockings for the prevention of venous leg ulcer recurrence: a health technology assessment. Ont Health Technol Assess Ser. 2019;19(2):1-86.

(20) Darvall KA, Bate GR, Adam DJ, Bradbury AW. Generic health-related quality of life is significantly worse in varicose vein patients with lower limb symptoms independent of CEAP clinical grade. Eur J Vasc Endovasc Surg. 2012;44(3):341-4.

(21) Michaels JA, Brazier JE, Campbell WB, MacIntyre JB, Palfreyman SJ, Ratcliffe J. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. Br J Surg. 2006;93(2):175-81.

(22) Sam RC, Darvall KA, Adam DJ, Silverman SH, Bradbury AW. A comparison of the changes in generic quality of life after superficial venous surgery with those after laparoscopic cholecystectomy. J Vasc Surg. 2006;44(3):606-10.

(23) Muller-Buhl U, Leutgeb R, Engeser P, Achankeng EN, Szecsenyi J, Laux G. Varicose veins are a risk factor for deep venous thrombosis in general practice patients. Vasa. 2012;41(5):360-5.

(24) Chang SL, Huang YL, Lee MC, Hu S, Hsiao YC, Chang SW, et al. Association of varicose veins with incident venous thromboembolism and peripheral artery disease. JAMA. 2018;319(8):807-17.

(25) Attaran RR. Latest innovations in the treatment of venous disease. J Clin Med. 2018;7(4).

(26) American College of Phlebology. Practice guidelines: superficial venous disease [Internet]. Chicago: The College; 2016 [cited 2019 Nov 5]. Available from: http://www.phlebology.org/wp-content/uploads/2016/02/SuperficialVenousDiseaseGuidelinesPMS313-02.03.16.pdf

(27) Gohel MS, Barwell JR, Earnshaw JJ, Heather BP, Mitchell DC, Whyman MR, et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study)--haemodynamic and anatomical changes. Br J Surg. 2005;92(3):291-7.

(28) Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53(5 Suppl):2S-48S.

(29) Hamdan A. Management of varicose veins and venous insufficiency. JAMA. 2012;308(24):2612-21.

(30) Ontario Health Technology Advisory Committee. OHTAC recommendation: endovasvular ablation for varicose veins [Internet]. Toronto: Health Quality Ontario; 2013 [cited 2019 Nov 5]. Available from: https://www.hqontario.ca/Portals/0/Documents/evidence/reports/recommendation-endovascular-ablation-varicose-veins-1307-en.pdf

(31) Medical Advisory Secretariat. Endovascular laser therapy for varicose veins: an evidence-based analysis. Ont Health Technol Assess Ser. 2010;10(6):1-92.

(32) Navarro TP, Delis KT, Ribeiro AP. Clinical and hemodynamic significance of the greater saphenous vein diameter in chronic venous insufficiency. Arch Surg. 2002;137(11):1233-7.

(33) National Institute for Health and Care Excellence. Cyanoacrylate glue occlusion for varicose veins (IPG 526) [Internet]. London (UK): The Institute; 2015 [cited 2019 Nov 8]. Available from: https://www.nice.org.uk/guidance/ipg526

(34) Gibson K, Minjarez R, Rinehardt E, Ferris B. Frequency and severity of hypersensitivity reactions in patients after VenaSeal cyanoacrylate treatment of superficial venous insufficiency. Phlebology. 2020;35(5):337-44.

(35) Food and Drug Administration. Devices@FDA [Internet]. Silver Spring (MD): The Administration; c2020 [cited 2020 8 May]. Available from: https://www.accessdata.fda.gov/SCRIPTS/cdrh/devicesatfda/index.cfm

(36) Ministry of Health and Long-Term Care. Schedule of benefits: physician services under the Health Insurance Act. Toronto (ON): Queen's Printer for Ontario; 2015. p. 746.
(37) National Institute for Health and Care Excellence. Cyanoacrylate glue occlusion for varicose veins. [IPG670]. 2020. Available from: https://www.nice.org.uk/guidance/ipg670
(38) Medical Services Advisory Committee. 1472– Cyanoacrylate embolisation for the treatment of varicose veins due to chronic venous insufficiency: public summary document [Internet]. Canberra (ACT): Commonwealth of Australia; 2017 [cited 2020 June 19]. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/47B770B24FA93321CA25810F001B4003/$File/1472-FinalPSD-accessible.pdf
(39) Belramman A, Bootun R, Onida S, Davis AH, Lane T. ClariVein®, mechanochemical endovenous ablation: patient selection and perspective. J Vasc Diagn Interv. 2019;7:1-8.
(40) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
(41) Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
(42) Covidence systematic review software. Veritas Health Innovation. Melbourne (Australia). Available at: https://www.covidence.org/home.
(43) WebPlotDigitizer [Computer program]. Version 4.3 California (USA): Ankit Rohatgi; July 2020. Available from: https://automeris.io/WebPlotDigitizer.
(44) Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen (DK): The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
(45) Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev. 1987;9:1-30.
(46) Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 2009;172(1):137-59.
(47) Cochrane Equity Methods Group. c2020. Evidence for equity: PROGRESS-Plus. Cited 30 July 2020. Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus.
(48) Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. Phlebology. 2016;31(1 Suppl):106-13.
(49) Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928.
(50) Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66(4):408-14.
(51) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): Grade Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
(52) Sun JJ, Chowdhury MM, Sadat U, Hayes PD, Tang TY. Mechanochemical ablation for treatment of truncal venous insufficiency: a review of the current literature. J Vasc Interv Radiol. 2017;28(10):1422-31.
(53) Witte ME, Zeebregts CJ, de Borst GJ, Reijnen M, Boersma D. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: a systematic review. Phlebology. 2017;32(10):649-57.
(54) Garcia-Carpintero E, Carmona M, Chalco-Orrego JP, Gonzalez-Enriquez J, Imaz-Iglesia I. Systematic review and meta-analysis of endovenous cyanoacrylate adhesive ablation for incompetent saphenous veins. J Vasc Surg. 2020;06:06.

(55) Vos CG, Unlu C, Bosma J, van Vlijmen CJ, de Nie AJ, Schreve MA. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. J Vasc Surg. 2017;5(6):880-96.
(56) Harlock JA, Elias F, Qadura M, Dubois L. Meta-analysis of nontumescent-based versus tumescent-based endovenous therapies for patients with great saphenous insufficiency and varicose veins. J Vasc Surg. 2018;6(6):779-87.e6.
(57) Hirsch T. Varicose vein therapy and nerve lesions. Vasa. 2017;46(2):96-100.
(58) Kugler NW, Brown KR. An update on the currently available nonthermal ablative options in the management of superficial venous disease. J Vasc Surg. 2017;5(3):422-9.
(59) Nugroho J, Wardhana A, Ghea C. Mechanical occlusion chemically assisted ablation (MOCA) for saphenous vein insufficiency: a meta-analysis of a randomized trial. Int J Vasc Med. 2020;2020:8758905.
(60) Dimech AP, Cassar K. Efficacy of cyanoacrylate glue ablation of primary truncal varicose veins compared to existing endovenous techniques: a systematic review of the literature. Surg J (N Y). 2020;6(2):e77-e86.
(61) Kolluri R, Chung J, Kim S, Nath N, Bhalla BB, Jain T, et al. Network meta-analysis to compare VenaSeal with other superficial venous therapies for chronic venous insufficiency. J Vasc Surg Venous Lymphat Disord. 2020;8(3):472-81 e3.
(62) Kubat E, Unal CS, Geldi O, Cetin E, Keskin A. What is the optimal treatment technique for great saphenous vein diameter of >=10 mm? Comparison of five different approaches. Acta Chir Belg. 2019:1-8.
(63) Yang GK, Parapini M, Gagnon J, Chen J. Comparison of cyanoacrylate (venaseal) and radiofrequency ablation for treatment of varicose veins in a Canadian population. J Vasc Surg. 2017;66 (3):e65.
(64) Bademci MS, Kocaaslan C, Aldag M, Yalvac ESD, Oztekin A, Bulut N, et al. Single-center retrospective review of early outcomes of radiofrequency ablation versus cyanoacrylate ablation of isolated great saphenous vein insufficiency. J Vasc Surg. 2019;7(4):480-5.
(65) Eroglu E, Yasim A. A randomised clinical trial comparing n-butyl cyanoacrylate, radiofrequency ablation and endovenous laser ablation for the treatment of superficial venous incompetence: two year follow up results. Eur J Vasc Endovasc Surg. 2018;56(4):553-60.
(66) Ovali C, Sevin MB. Twelve-month efficacy and complications of cyanoacrylate embolization compared with radiofrequency ablation for incompetent great saphenous veins. J Vasc Surg. 2019;7(2):210-6.
(67) McGuinness B, Elias F, Ali KP, Ahmad MS, Namburi J, Chan B, et al. A comparison of duplex ultrasound findings after cyanoacrylate embolization versus endovenous laser ablation of the great saphenous vein. J Vasc Surg. 2019;7(6):824-31.
(68) Koramaz I, El Kilic H, Gokalp F, Bitargil M, Bektas N, Engin E, et al. Ablation of the great saphenous vein with nontumescent n-butyl cyanoacrylate versus endovenous laser therapy. J Vasc Surg. 2017;5(2):210-5.
(69) Gibson K, Morrison N, Kolluri R, Vasquez M, Weiss R, Cher D, et al. Twenty-four month results from a randomized trial of cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. J Vasc Surg. 2018;6(5):606-13.
(70) Morrison N, Gibson K, McEnroe S, Goldman M, King T, Weiss R, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg. 2015;61(4):985-94.
(71) Morrison N, Gibson K, Vasquez M, Weiss R, Cher D, Madsen M, et al. VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. J Vasc Surg. 2017;5(3):321-30.

(72) Morrison N, Kolluri R, Vasquez M, Madsen M, Jones A, Gibson K. Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36-month outcomes of the VeClose randomized controlled trial. Phlebology. 2019;34(6):380-90.
(73) Bootun R, Lane TR, Dharmarajah B, Lim CS, Najem M, Renton S, et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: the multicentre Venefit versus ClariVein for varicose veins trial. Phlebology. 2016;31(1):61-5.
(74) Lane T, Bootun R, Dharmarajah B, Lim CS, Najem M, Renton S, et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins -- final results of the Venefit versus Clarivein for varicose veins trial. Phlebology. 2017;32(2):89-98.
(75) van Eekeren RR, Boersma D, Konijn V, de Vries JP, Reijnen MM. Postoperative pain and early quality of life after radiofrequency ablation and mechanochemical endovenous ablation of incompetent great saphenous veins. J Vasc Surg. 2013;57(2):445-50.
(76) Vun SV, Rashid ST, Blest NC, Spark JI. Lower pain and faster treatment with mechanico-chemical endovenous ablation using ClariVein. Phlebology. 2015;30(10):688-92.
(77) Moon KH, Dharmarajah B, Bootun R, Lim CS, Lane T, Moore HM, et al. Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins. Phlebology. 2017;32(6):425-32.
(78) Kim SY, Safir SR, Png CYM, Faries PL, Ting W, Vouyouka AG, et al. Mechanochemical ablation as an alternative to venous ulcer healing compared with thermal ablation. J Vasc Surg. 2019;7(5):699-705.
(79) Holewijn S, van Eekeren R, Vahl A, de Vries J, Reijnen M, group Ms. Two-year results of a multicenter randomized controlled trial comparing mechanochemical endovenous ablation to radiofrequency ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial). J Vasc Surg. 2019;7(3):364-74.
(80) Vahaaho S, Mahmoud O, Halmesmaki K, Alback A, Noronen K, Vikatmaa P, et al. Randomized clinical trial of mechanochemical and endovenous thermal ablation of great saphenous varicose veins. Br J Surg. 2019;106(5):548-54.
(81) Morrison N, Gibson K, Vasquez M, Weiss R, Jones A. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord. 2020.
(82) Kubat E, Unal CS, Geldi O, Cetin E, Keskin A, Karapinar K. Comparison of different approaches to small saphenous vein reflux treatment: a retrospective study in two centers. Sao Paulo Med J. 2020;138(2):98-105.
(83) Mohamed AH, Leung C, Wallace T, Smith G, Carradice D, Chetter I. A randomized controlled trial of endovenous laser ablation versus mechanochemical ablation with ClariVein in the management of superficial venous incompetence (LAMA Trial). Ann Surg. 2020.
(84) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(6):e1000097.
(85) Vahaaho S, Halmesmaki K, Mahmoud O, Alback A, Noronen K, Venermo M. Three-year results of a randomized controlled trial comparing mechanochemical and thermal ablation in the treatment of insufficient great saphenous veins. J Vasc Surg Venous Lymphat Disord. 2020.
(86) Passman MA, McLafferty RB, Lentz MF, Nagre SB, Iafrati MD, Bohannon WT, et al. Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National Venous Screening Program. J Vasc Surg. 2011;54(6 Suppl):2S-9S.

(87) Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg. 2010;52(5):1387-96.
(88) Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH. Towards measurement of outcome for patients with varicose veins. Qual Health Care. 1993;2(1):5-10.
(89) Staniszewska A, Tambyraja A, Afolabi E, Bachoo P, Brittenden J. The Aberdeen varicose vein questionnaire, patient factors and referral for treatment. Eur J Vasc Endovasc Surg. 2013;46(6):715-8.
(90) Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
(91) EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
(92) Ay Y, Gunes E, Turkkolu ST, Selcuk E, Calim M, Akal R, et al. Comparative efficacy and life quality effects of surgical stripping, radiofrequency ablation, and cyanoacrylate embolization in patients undergoing treatment for great saphenous vein insufficiency. Phlebology. 2020:Epub ahead of print. PMID: 32741257. DOI 10.1177/0268355520947292.
(93) Le Moine JG, Fiestas-Navarrete L, Katumba K, Launois R. Psychometric validation of the 14 items ChronIc Venous Insufficiency Quality of Life Questionnaire (CIVIQ-14): confirmatory factor analysis. Eur J Vasc Endovasc Surg. 2016;51(2):268-74.
(94) National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance. 3rd ed. London (UK): The Institute; 2012. Appendix I, quality appraisal checklist—economic evaluations.
(95) Inderhaug E, Schelp CH, Glambek I, Kristiansen IS. Cost-effectiveness analysis of five procedures for great saphenous vein reflux in a Norwegian healthcare setting or societal setting. SAGE Open Med. 2018;6:2050312118801709.
(96) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(97) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): The Agency; 2017. p. 76.
(98) IntelliHealth Ontario. National Ambulatory Care Reporting System database [Internet]. Toronto (ON): Queen's Printer for Ontario; c2012-2013 [cited 2020 Feb 14]. Available from: https://www.ihbi.health.gov.on.ca/ibmcognos
(99) Institute of Health Economics. Endovenous ablation interventions for symptomatic varicose veins of the legs. Edmonton (AB): The Institute; 2014.
(100) Tassie E, Scotland G, Brittenden J, Cotton SC, Elders A, Campbell MK, et al. Cost-effectiveness of ultrasound-guided foam sclerotherapy, endovenous laser ablation or surgery as treatment for primary varicose veins from the randomized CLASS trial. Br J Surg. 2014;101(12):1532-40.
(101) Lane TR, Kelleher D, Shepherd AC, Franklin IJ, Davies AH. Ambulatory varicosity avulsion later or synchronized (AVULS): a randomized clinical trial. Ann Surg. 2015;261(4):654-61.
(102) Statistics Canada. Life tables, Canada, provinces and territories [Internet]. Ottawa (ON): Statistics Canada; 2020 [cited 2020 Feb 18]. Available from: https://www150.statcan.gc.ca/n1/en/catalogue/84-537-X
(103) Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford (UK): Oxford University Press; 2006.

(104) Consumer Price Index, annual average, not seasonally adjusted [Internet]. Ottawa (ON): Statistics Canada; 2020 [updated 2020; cited 2020 Aug 20]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501

(105) Ministry of Health and Long-Term Care. Health data branch web portal: Ontario case costing [Internet]. Toronto (ON): Queen's Printer for Ontario. 2017 [cited 2020 Feb]. Available from: https://hsim.health.gov.on.ca/HDBPortal

(106) Butt A, Kopriva D. Economic implications of endovenous great saphenous ablation in a public health care system. J Vasc Surg Venous Lymphat Disord. 2018;6(4):471-6 e6.

(107) Government of Canada. Compare wages: registered nurses and registered psychiatric nurses [Internet]. 2020 [updated 2019 Nov 27; cited 2020 Feb 5]. Available from: https://www.jobbank.gc.ca/wagereport/occupation/993

(108) Xie X, Wang M, Schaink A, Krahn M. Pulmonary rehabilitation for postacute exacerbations of chronic obstructive pulmonary disease (COPD): a cost-effectiveness and budget impact analysis. Toronto (ON): Queen's Printer for Ontario; 2015 Feb.

(109) College of Physicians and Surgeons of Ontario. Out-of-hospital premises inspection program [Internet]. Toronto (ON): The College; 2020 [cited 2020 Feb 18]. Available from: https://www.cpso.on.ca/Physicians/Your-Practice/Quality-in-Practice/Clinic-Inspections-Special-Programs/Out-of-Hospital-Premises-Inspection-Program

(110) Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health. 2008;11(5):886-97.

(111) O'Flynn N, Vaughan M, Kelley K. Diagnosis and management of varicose veins in the legs: NICE guideline. Br J Gen Pract. 2014;64(623):314-5.

(112) Canadian Institute for Health Information. Canadian classification of health interventions — tabular list. Ottawa (ON): 2015.

(113) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.

(114) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.

(115) Ontario Health Technology Advisory Committee Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 Apr [cited 2018 Apr 30]. Available from: http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf

(116) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.

(117) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33–45.

(118) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.

(119) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.

(120) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.

(121) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr

30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf

(122) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.

(123) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.

(124) NVivo qualitative data analysis software. QSR International. Doncaster, Victoria (Australia). Available at: https://www.qsrinternational.com/nvivo/home.

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