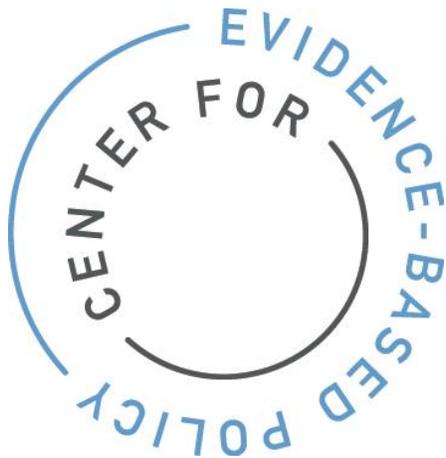


Mechanochemical Venous Ablation for Varicose Veins

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Overview

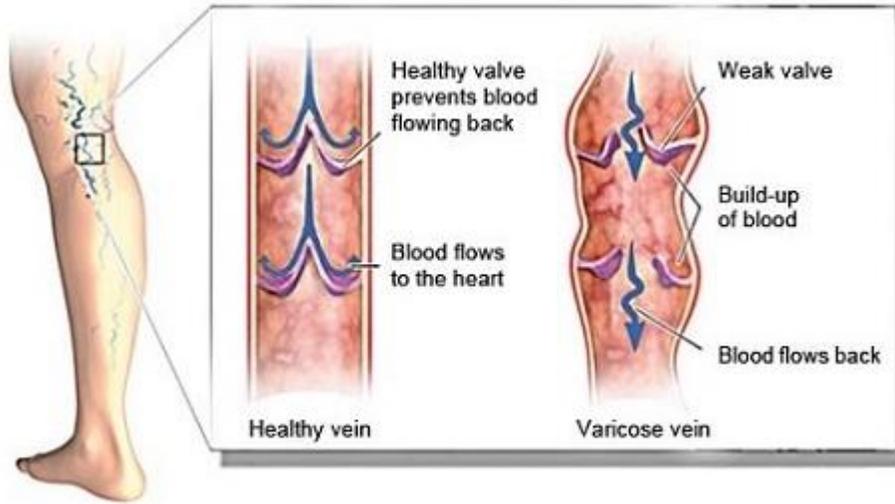
Mechanochemical ablation is a newer approach to address varicose veins, a common sign of chronic venous disorder, causing cosmetic changes, pain, and other symptoms in the legs such as a feeling of heaviness or leg cramps for many individuals. This review is limited to evidence, policy, and clinical practice guidelines on the use of mechanochemical ablation (MOCA) for varicose veins. The comparative effectiveness of non-mechanochemical approaches for varicose veins is outside the scope of this review.

Background

Clinical Overview

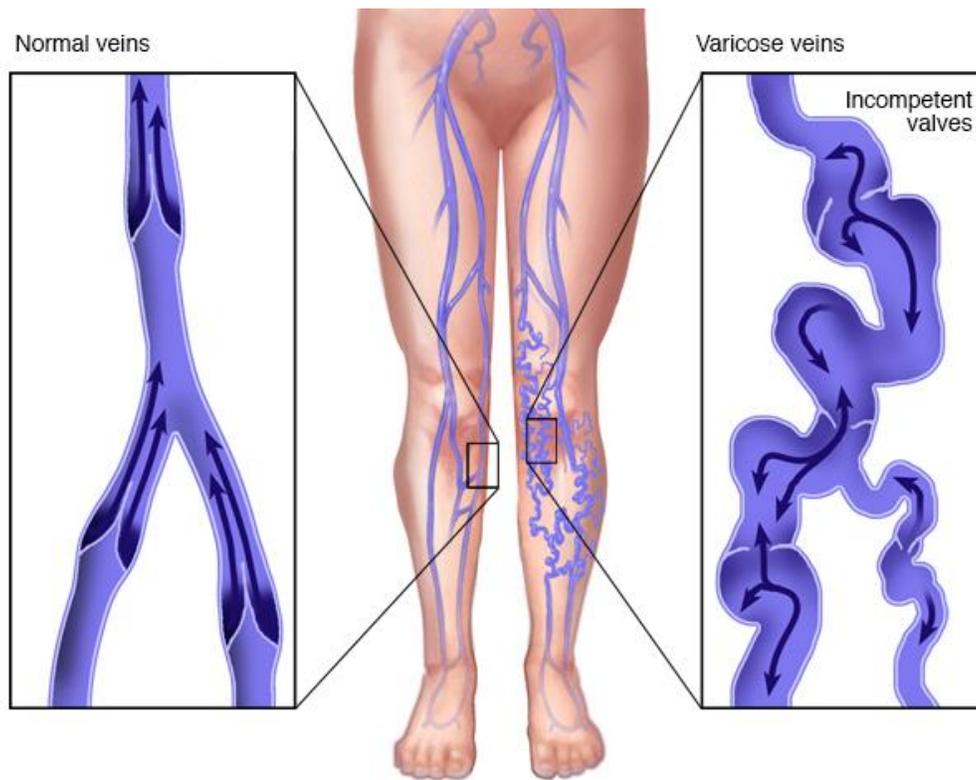
Varicose veins are a common finding of chronic venous disorder, estimated to affect nearly 20% of adults (Eklof, Perrin, Delis, Rutherford, & Gloviczki, 2009; Institute for Quality and Efficiency in Health Care, 2008). Individuals might be asymptomatic or develop symptoms ranging from cosmetic changes (e.g., webs of dark veins appearing purple or blue) to muscle cramps, itching, and pain. The physical appearance of the veins is not correlated with their health effects (i.e., larger veins aren't necessarily more painful or more severe). Varicose veins occur when the valves within the veins become leaky and blood pools downstream, away from the heart, causing swelling of the vein (Figures 1 and 2) (Institute for Quality and Efficiency in Health Care, 2008). Some individuals might develop chronic venous insufficiency, with leg edema, skin changes, or venous ulcers (Eklof et al., 2009). Veins can be assessed by ultrasound to determine the presence and severity of reflux (i.e., backwards blood flow) across a vein valve and the length of time the reflux occurs. Obesity, family history of varicose veins, pregnancy, inactivity, prolonged sitting or standing, and older age are risk factors for developing the condition (Washington Health Technology Assessment Program, 2017).

Figure 1. Varicose Vein Etiology



Source. Institute for Quality and Efficiency in Health Care (2008).

Figure 2. Normal Veins Compared to Varicose Veins



Source. Mayo Clinic (2017)

The most commonly affected veins are the great saphenous vein and the small (or lesser) saphenous vein. The CEAP (clinical, etiology, anatomy, and pathophysiology) classification system describes the severity of chronic venous disorder. Although the etiology, anatomy, and pathophysiology components of CEAP are relevant, the clinical assessment portion is most often used to describe chronic venous disorders on a scale of zero (no signs of venous disease) to six (active open ulcer).

Common patient-reported assessment tools for severity of varicose veins are the Aberdeen Varicose Vein Questionnaire ([AVVQ](#)) (scored zero to 100, with higher scores signifying more negative effects), and the Venous Clinical Severity Score (VCSS), which is an expansion of the CEAP (scored zero to 30, with higher scores signifying more negative effects) (National Institute for Health and Care Excellence [NICE], 2016; Vasquez & Munschauer, 2008). Additional information on vein classification tools is in Appendix A. A recent systematic review on patient-reported outcomes measures for individuals with varicose veins noted that although the AVVQ is a validated scale, the available evidence relies on clinician opinion, which could bias results (Aber et al., 2017).

Techniques used to address varicose veins range from compression stockings and lifestyle changes for individuals with lower clinical disease scores (e.g., spider veins, non-painful varicose veins with or without edema) to invasive surgery (Institute for Quality and Efficiency in Health Care, 2008). Individuals who experience pain, swelling (not improved with compression or lifestyle changes), or development of ulcers might be evaluated by a specialist (e.g., vascular surgeon) to determine whether an intervention is warranted. Table 1 provides descriptions of common approaches to treat varicose veins. Interventional approaches aim to collapse the vein entirely or remove it (e.g. stripping), and vary in the amount of anesthesia needed.

Table 1. Overview of Treatment Approaches for Varicose Veins

Approach	Description
Compression stockings, elevation, lifestyle modifications, weight loss	Non-interventional approaches Lack of adherence may limit efficacy
Endovenous obliteration (e.g., MOCA, RFA, endovenous laser ablation)	May use heat, radio waves, chemical agent, or a laser to scar the vein or coagulate blood in the vein to close it
Sclerotherapy	Chemical agent injected into the vein to scar and close it off
Ligation	Small veins are tied off as they branch off larger ones
Phlebectomy	Small 1–2mm incisions over the entire vein, with the vein pulled to the surface and removed after closure upstream

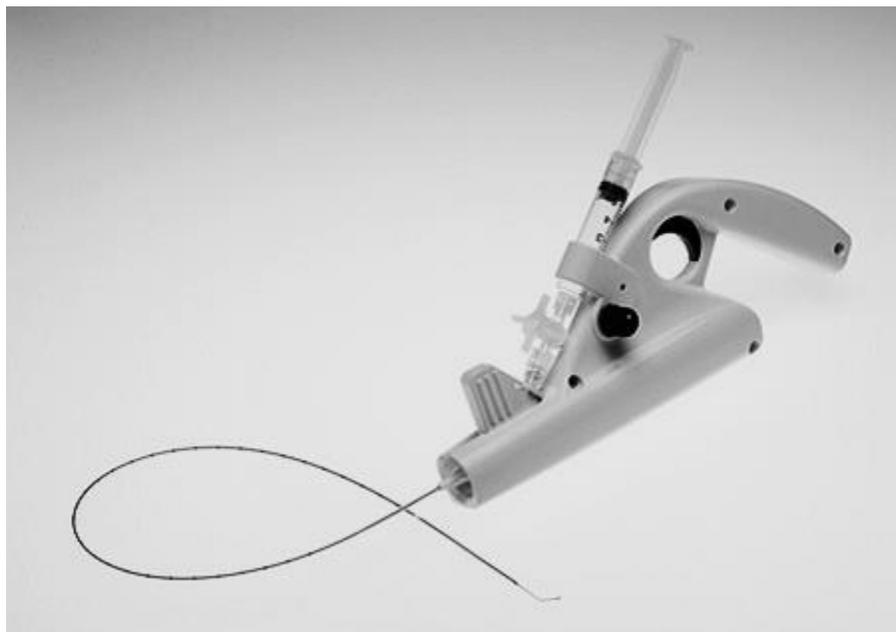
Stripping	Removal of the saphenous vein
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Abbreviations. MOCA: mechanochemical ablation; RFA: radiofrequency ablation. Source. Adapted from Jones and Carek (2008).

MOCA is an endovenous obliteration technique using a catheter to advance a rotating wire that irritates the lining of the vein while simultaneously infusing a sclerosant or chemical agent that aids in closing the vein. MOCA devices are classified as a continuous flush catheter and designated as Class II devices by the U.S. Food and Drug Administration (FDA) (FDA, 2008). Figure 3 shows an example of a MOCA device.

MOCA is billed using the Current Procedural Terminology (CPT) codes 36473 (endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated) and 36474 (endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; subsequent vein(s) treated in a single extremity, each through separate access sites).

Figure 3. MOCA Example



Source. Elias and Raines (2012, p. 68).

Key Findings

- There are no comparative studies on MOCA versus conservative therapy (e.g., compression stockings, lifestyle changes, weight loss). With the exception of radiofrequency ablation (RFA), randomized comparative data to other interventional procedures is lacking.

Limitations of the available evidence include bias from small sample sizes, reliance on nonrandomized studies, heterogeneity in protocols for the chemical component, and industry funding.

- Participants in studies all had varicose veins and either demonstrated vein insufficiency (i.e. reflux on Doppler ultrasound) or met inclusion criteria based on size of the varicose vein (e.g. length or width of varicose vein). The CEAP score ranged from two to six but was not reported in all studies.
- A single randomized controlled trial (RCT) comparing MOCA to RFA reported similar occlusion rates, symptom severity, and quality-of-life scores at six months post-procedure.
- Nonrandomized comparative studies reported that MOCA recipients are on average able to return to work a day sooner than RFA recipients and experience similar rates of complications compared to RFA (e.g., bleeding).
- One recently published clinical practice guideline, which was of poor methodological quality, recommended the use of MOCA for the treatment of varicose veins, but noted that additional long-term follow-up data are needed. This recommendation is based on the single available poor methodological quality RCT comparing MOCA to RFA.
- There is discordance across payers reviewed for this report; federal, state Medicaid, and private payers vary in their coverage of MOCA. Eight of the ten private payers searched consider MOCA investigational, experimental, and/or unproven and do not cover the procedure. The CPT codes (36473, 36474) for MOCA are included in the Medicare and five of the nine state Medicaid agency fee schedules searched for this report, but no explicit coverage criteria were available. Three out of nine state Medicaid agencies (Florida, New York, Pennsylvania) searched do not provide coverage criteria regarding MOCA in their provider manuals, nor are the applicable CPT codes listed in their respective fee schedules.

PICO

The following PICO guides this evidence review.

Population: Individuals with symptomatic lower extremity chronic venous disease

Intervention: Mechanochemical ablation

Comparators: Conservative therapy (e.g., compression, leg elevation); other endovenous ablation therapies (e.g., laser, radiofrequency); sclerotherapy; surgery (e.g., ligation/stripping, phlebectomy)

Outcomes: Symptom resolution, quality of life, function, time to complete healing, incidence of repeat procedure or other procedures, adverse events, economic outcomes (e.g., cost, cost-effectiveness)

Methods

Center for Evidence-based Policy (Center) researchers searched Center core evidence and guidelines sources and Ovid MEDLINE for systematic reviews (with or without meta-analysis), and technology assessments on MOCA published within the last 10 years and clinical practice guidelines published within the last five years. Search dates for individual studies were determined by the last search dates of the included systematic reviews. Center researchers additionally searched the Ovid MEDLINE database for individual studies published between January 1, 2016 and September 30, 2017. Center researchers evaluated the methodological quality of systematic reviews, individual studies, and clinical practice guidelines eligible for this report using the methodology described in detail in Appendix B and quality assessment tools included with the New York State Department of Health dossier process (available on pages 14 to 33 of the *Dossier Submission Form* located on the New York State Department of Health [website](#)). Center researchers also searched Medicare, several state Medicaid programs, and private payers for coverage policies on MOCA for varicose veins. See Appendix B for a full list of payers searched.

Center researchers excluded systematic reviews if all of the included studies were also summarized by a more comprehensive systematic review, a systematic review of a higher methodological quality, and/or a more recently published systematic review. Patient-important outcomes that have relevance for New York State Department of Health, provided in the PICO section above, were predetermined in the topic scope development, and studies reporting other outcomes were not included. Excluded outcomes include histological findings, biological markers, technical success without follow-up, and procedure time. Exclusion criteria were selected prior to review of the studies, and study methods were assessed prior to review of outcomes to eliminate bias. See Appendix B for a full description of methods.

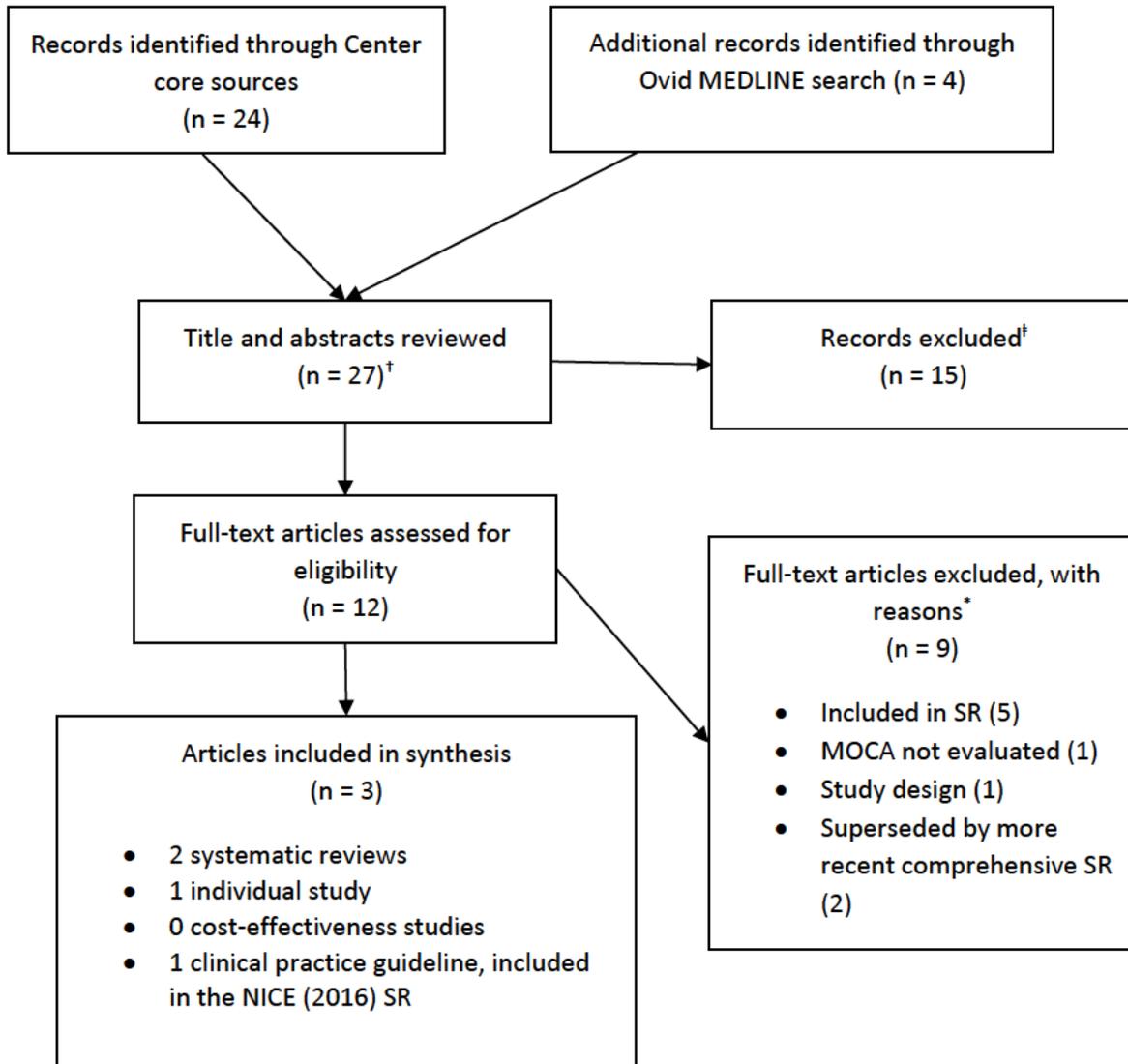
Evidence Review

Findings

Center researchers identified two systematic reviews (NICE, 2016; Witte, Zeebregts, de Borst, Reijnen, & Boersma, 2017b) and one RCT (Lane et al., 2017) on MOCA for varicose veins. Figure 4 outlines the number of articles identified by each search and the total number of studies included in this evidence synthesis. The systematic review from NICE (2016) includes clinical practice guidance, and therefore is included in both the effectiveness and guideline sections of this report. Multiple systematic reviews included identical studies; thus, the most up-to-date and highest quality methodological studies are included in this report.

The search strategies and list of studies reviewed in full with reasons for exclusion are in Appendices B and C, respectively.

Figure 4. Search Results



Abbreviations. MOCA: mechanochemical ablation; SR: systematic review.

† One duplicate citation identified between Center core source search and Ovid MEDLINE search results.

‡ Articles were excluded if they did not meet predetermined inclusion criteria (e.g., PICO, study design, English language, publication date) as described in Appendix B.

* Exclusion rationale provided in Appendix C.

Overview of Evidence Sources

Systematic Reviews

NICE (2016)

NICE (2016) conducted a fair methodological quality systematic review identifying efficacy and safety evidence on MOCA for individuals with varicose veins. Comparative and non-comparative studies were included. The review authors used an extensive search strategy (e.g., multiple databases searched, comprehensive search strategy used, few to no limits on study publication date); they searched databases from inception¹ to February 2016 to identify nine studies: a single RCT, two nonrandomized comparative studies, five case series, and a case report on harm (NICE, 2016). The systematic review provided a narrative description of included studies.

Participants in the included studies were often female, with a mean age of 49 to 59 years, and with symptomatic varicose veins of the lower extremities (NICE, 2016). Additional details of participants (e.g., comorbidities) are not included in the systematic review. The criteria defining symptomatic varicose veins was not consistent across the included studies; diameter or length of the varicose vein, CEAP score of C2 to C6, or presence of reflux on Doppler ultrasound were all used to determine participant eligibility (NICE, 2016). The authors did not use a formal quality assessment tool, but noted that the estimate of efficacy for the procedures was limited by short follow-up periods (two years at most) and variations in chemical agents and dosage within and across studies (NICE, 2016).

The single RCT identified in this systematic review, Bootun et al. (2016),² is the preliminary data from the multicenter Venefit versus ClariVein for varicose veins trial. The final data from this RCT was published in Lane et al. (2017). Because this is the sole randomized comparative data source for MOCA and the NICE (2016) systematic review does not include the final outcomes, Center researchers elected to review the individual study (Lane et al., 2017) (see page 9).

Witte et al. (2017b)

Witte et al. (2017b) conducted a poor methodological quality systematic review on MOCA as a treatment for great and small saphenous vein insufficiency. The primary outcome of interest reported in the review, anatomical success at time of the procedure (i.e., absence of reflux on ultrasound), is not a patient-centered outcome because the systematic review authors did not report any follow-up on maintenance of this finding beyond the day of procedure. Additional outcomes meeting inclusion criteria for this systematic review included clinical success (e.g., VCSS, AVVQ) and major complications (Witte et al., 2017b).

¹ Inception dates vary across databases. For example, the inception date for Ovid MEDLINE is 1946 (Ovid, 2017) and for PsychINFO it is 1597, although comprehensive coverage starts in the 1880s (American Psychological Association, 2017).

² Identified in the systematic review as Bootun et al. (2014) because it was an e-publication ahead of print.

The review authors used an extensive search strategy (e.g., multiple databases searched, comprehensive search strategy used, few to no limits on study publication date) to identify 13 publications on 10 cohorts of patients (six case series, two nonrandomized comparative studies, two RCTs). The systematic review does not provide demographic (e.g., age, gender) or clinical baseline data (e.g., comorbidities, clinical severity) across the included studies (Witte et al., 2017b). One RCT randomized participants to differing doses of polidocanol, the sclerosant chemical, rather than a procedure (Lam, Toonder, & Wittens, 2016). Only data from the MOCA arm of the multicenter Venefit versus ClariVein for varicose veins RCT (Lane et al., 2017) was reported, so Center researchers elected to review the study in full to review comparative effectiveness findings, if present.

Individual Studies

Lane et al. (2017)

Lane et al. (2017) conducted a poor methodological quality RCT on MOCA compared to RFA on a total of 170 individuals with a primary outcome of procedure-related pain. Eligible participants were adults (> 18 years) and demonstrated reflux of the saphenous veins (\geq 0.5 seconds). Over half of participants (58.8%) were female, and 13.4% had a body mass index over 30. Study participants presented with primary symptomatic varicose veins of the great saphenous vein (86.5%), with a median score of 4 on CEAP (i.e., skin changes without ulceration). Mean scores of clinical severity reflected mild severity (AVVQ mean of 19 on a scale of zero to 100; VCSS mean of three on a scale of zero to 27). The chemical sclerosant used in MOCA was 2% sodium tetradecyl sulphate. Preliminary results from 117 individuals (119 legs) were reported in Bootun et al. (2016) and included in the NICE (2016) systematic review. Final results were published in Lane et al. (2017). Loss to follow-up was high across both arms (greater than 20% at one and six months).

Quality and Limitations

Center researchers rated one of the systematic reviews as having fair methodological quality (NICE, 2016) and one as having poor methodological quality (Witte et al., 2017b). There was significant overlap of included studies across the two systematic reviews. Witte et al. (2017b) searched through October 2016, eight months later than the NICE (2016) review. Witte et al. (2017b) identified two updates to previous case series (Kim et al., 2017; Witte et al., 2017a), a new case series (Tang, Kam, & Gaunt, 2017), and an update from the sole RCT (Lane et al., 2017).

Witte et al. (2017b) noted the lack of long-term data, high loss to follow-up (50%), heterogeneity of definitions for occlusion (e.g., clinical success) in the follow-up period, and absence of RCTs as limitations to the available evidence that introduce potential bias into the findings. Only one study described an a priori power analysis, with sufficient enrollment achieved to detect a 20% difference in procedure-related pain between RFA and MOCA

recipients (Bootun et al., 2016). In the sole RCT comparing MOCA to RFA (Lane et al., 2017), more than two-thirds of participants received phlebectomy immediately after MOCA or RFA, limiting the ability to attribute findings of quality of life or symptom severity scoring to MOCA or RFA alone.

Summary of the Evidence

Table 2 provides a high-level summary of the evidence listed by systematic review and included studies. The overall methodological quality of the systematic reviews (NICE, 2016; Witte et al., 2017b) and the RCT (Lane et al., 2017) are the Center's original assessment of the studies. For systematic reviews, the authors' quality assessment of included studies is in the second column.

Table 2. Overview of Included Studies

Citation, Study Details	# of Studies (k) Population (n) <i>Individual Study Quality</i>	Study Summary and Findings	Comments
Systematic Reviews (without Meta-analyses)			
<p>NICE (2016)</p> <p><u>Search Dates</u> Database inception to February 2016</p> <p><u>Eligible Study Designs</u> Clinical studies with efficacy or safety outcomes</p> <p><u>Methodological Quality (assessed by Center researchers)</u> Fair</p>	<p>K = 9 (1 RCT, 2 nonrandomized comparative studies, 5 case series, 1 case report)</p> <p>Total n = 930</p> <p><i>Methodological quality of included studies (assessed by the SR authors):</i> Not formally assessed but noted available evidence with limited validity and generalizability stemming from short follow-up, heterogeneity across protocols for sclerosant, and use</p>	<p><u>Comparators</u> MOCA vs. RFA or EVLT</p> <p><u>Outcomes (Effectiveness from 2 nonrandomized comparative studies)</u></p> <p><i>Median procedure-related pain (VAS) (n = 147)</i> MOCA = 1 vs. RFA = 5 vs. EVLT = 6, (p < 0.01)</p> <p><i>VCSS (IQR) at 6 weeks (n = 68)</i> MOCA 1 (IQR, 1.0 to 2.0) vs. RFA: 3.0 (IQR, 1.25 to 3.75) p = .21</p> <p><i>AVVQ (IQR) at 6 weeks (n = 68)</i> MOCA: 5.0 (IQR, 3.0 to 8.5) vs. RFA: 4.5 (IQR, 1.5 to 11.2) p = .17</p> <p><i>Time to return to work (IQR) (n = 92)</i> MOCA: 1.0 day (IQR, 0 to 3.75) vs. RFA: 2.0 (IQR, 2 to 7) p = 0.02</p> <p><i>Complications (MOCA vs. RFA)</i> No statistically significant differences for the following complications: hematoma (6% vs. 12%),</p>	<p>This review included preliminary outcome data from a single RCT (Bootun et al., 2016). Because the final effectiveness and harms data from this trial is available and included as an individual study (Lane et al., 2017), it is not described here.</p> <p>Different chemical sclerosants and different doses were used across studies.</p> <p>Data presented in this section derive from nonrandomized comparative studies of short durations.</p> <p>Studies included individuals with small or great saphenous vein disease.</p> <p>The VCSS and AVVQ are common quality of life and symptom severity tools in the varicose vein literature. Appendix A includes additional information on these tools.</p> <p>Loss to follow-up ranged from 2% to 42% across included studies.</p>

Citation, Study Details	# of Studies (k) Population (n) <i>Individual Study Quality</i>	Study Summary and Findings	Comments
	of concomitant procedures.	<p>paresthesia (0% vs. 0%), thrombophlebitis (0% vs 6%), swelling (12% vs. 24%), hyperpigmentation (9% vs. 9%)</p> <p><u>Harms (from case series or case report)</u></p> <p><i>Deep vein thrombosis or pulmonary emboli</i> 1 DVT and 2 pulmonary emboli in a case series of 449</p> <p><i>Nerve injury</i> 1 sural nerve injury in case series of 449</p> <p><i>Thrombophlebitis</i> 2% to 13% of MOCA recipients</p> <p><i>Pain: Swelling at injection site or of limb</i> 1% (case series n = 449) to 18% (case series n = 73) of MOCA recipients</p> <p><i>Infection</i> Abscess or infection at puncture site reported in two case series: 1 out of 449, 1 out of 147</p> <p><i>Inadvertent stripping</i></p>	<p>Authors in 2 of the 9 publications noted industry financial connections from the ClariVein manufacturer.</p> <p>For time to return to work, it is unclear whether all participants were working prior to procedure.</p>

Citation, Study Details	# of Studies (k) Population (n) <i>Individual Study Quality</i>	Study Summary and Findings	Comments
		Single case report of inversion stripping as device fixed to a calcified venous tributary and vein came out as device removed.	
<p>Witte et al. (2017b)</p> <p><u>Search Dates</u> October 2016, lower end date not reported</p> <p><u>Eligible Study Designs</u> Clinical studies with efficacy or safety outcomes</p> <p><u>Methodological Quality (assessed by Center researchers)</u> Poor</p>	<p>k = 10 studies (13 publications; 1 RCT, 1 RCT of sclerosant dose, 6 case series, 2 nonrandomized comparative)</p> <p>Total n = 1,521 veins</p> <p><i>Methodological quality of included studies (assessed by the SR authors):</i></p> <p>Authors reported all studies are of moderate to good quality using the MINORS* scoring scale</p>	<p><u>Harms (major complications in MOCA recipients)</u></p> <p><i>DVT (9 studies)</i> 3 reported from 1,464 procedures (0.2%)</p> <p><i>Pulmonary Embolism (9 studies)</i> 2 reported from 1,464 procedures (0.1%)</p> <p><i>Paresthesia (9 studies)</i> 1 reported from 1,464 procedures (<0.1%)</p>	<p>Authors did not include findings from comparator groups; thus, only harms, rather than effectiveness data, are provided here.</p> <p>Authors reported population by number of veins, not number of individuals, thus an individual could be counted multiple times.</p> <p>Authors did not report on study population characteristics.</p> <p>Authors used a quality tool for nonrandomized studies to assess quality of randomized studies.</p> <p>Five studies had greater than 5% of loss to follow-up (exact numbers not provided).</p> <p>Authors in 6 of the 13 publications noted industry financial connections from the ClariVein manufacturer.</p> <p>The authors noted "effect of MOCA on generic QoL scores was limited." Additional information was not provided.</p>

Citation, Study Details	# of Studies (k) Population (n) <i>Individual Study Quality</i>	Study Summary and Findings	Comments
			Included studies used polidocanol or sodium tetradecyl sulphate (sotradecol) as the chemical sclerosant agent and used differing doses across studies and within the same study.
Randomized Controlled Trial			
<p>Multicenter Venefit versus ClariVein for varicose veins trial</p> <p>Reported in: Bootun et al. (2016); Lane et al. (2017)</p> <p><u>Follow-up</u> 6 months</p> <p><u>Location</u> UK</p> <p><u>Methodological Quality (assessed by Center researchers)</u> Poor</p>	<p>n = 170</p> <p>Included: Adults with primary great saphenous or small saphenous venous incompetence (reflux >0.5 seconds)</p> <p>Excluded: Individuals with recurrent varicose veins, current DVT, arterial insufficiency, hypercoagulopathy, unwilling to participate or complete surveys</p>	<p><u>Comparators</u> MOCA vs. RFA</p> <p><u>Outcomes</u> <i>Average pain during ablation (VAS)</i> 10 mm (3 to 25 mm) vs. 19.5 mm (9 to 38 mm) p = 0.003</p> <p><i>No significant differences between groups at six months for disease-specific quality of life (AVVQ); general quality of life; VCSS; time to return to work or normal activities; technical success (complete or proximal occlusion).</i></p> <p><i>Phlebitis</i> 3 MOCA vs. 2 RFA</p> <p><i>DVT</i> 1 in each group</p>	<p>Study powered to detect a 20 mm change in procedure-related pain score.</p> <p>High loss to follow-up at 1 and 6 months (>20%).</p> <p>74% of participants underwent phlebectomy immediately after MOCA or RFA.</p> <p>RFA recipients underwent tumescent anesthesia (extensive infiltration with 400 ml of local anesthesia around the vein) prior to ablation; MOCA recipients did not. However, because nearly three quarters of MOCA recipients subsequently underwent phlebectomy, they would have had tumescent anesthesia performed, so although they may have experienced less pain from the ablation, they ultimately experienced the more painful procedure, tumescent anesthesia.</p>

Abbreviations. AVVQ: Aberdeen Varicose Vein Questionnaire; DVT: deep vein thrombosis; EVLT: endovenous laser treatment; IQR: interquartile range;

*MOCA; mechanochemical ablation; QoL: quality of life; RCT: randomized controlled trial; RFA: radiofrequency ablation; SR: systematic review; VAS: visual analogue scale; VCSS: venous clinical severity score. Note: * The MINORS scoring system is a methodological index for nonrandomized studies. It includes consideration of patient inclusion criteria, prospective collection of data, appropriateness of study endpoints, role of bias in study endpoint assessment, appropriateness of follow-up periods, percent of population lost to follow-up, prospective calculation of sample size, adequacy of control group, baseline equivalence of groups, and adequateness of statistical analyses (Witte et al., 2017b).*

Effectiveness: Occlusion Rates at Six or More Months Post-Procedure

Systematic Reviews

A single systematic review (NICE, 2016) included occlusion rates reported at six months or more after MOCA, but the findings were derived from non-comparative case series. Three case series reported on occlusion rates; estimates ranged from 88% to 95% at 12 months post-procedure.

Individual Studies

Lane et al. (2017) reported on partial or full occlusion rates at six months post-procedure and did not observe statistically significant differences between RFA and MOCA recipients.

Effectiveness: Quality of Life (AVVQ) at Six Weeks

Systematic Reviews

A single systematic review (NICE, 2016) reported on quality of life at six weeks post-procedure (as assessed using the AVVQ) for MOCA compared to RFA from a single nonrandomized comparative study. There was no statistically significant difference in quality of life between MOCA and RFA recipients.

Individual Studies

Lane et al. (2017) reported on AVVQ scores at six months post-procedure and did not observe statistically significant differences between RFA and MOCA recipients.

Effectiveness: Symptom Severity (VCSS)

Systematic Reviews

A single systematic review (NICE, 2016) reported on symptom severity at six weeks post-procedure (as assessed using the VCSS) for MOCA compared to RFA from a single nonrandomized comparative study. There was no statistically significant difference in symptom severity between MOCA and RFA recipients.

Individual Studies

Lane et al. (2017) reported VCSS at six months post-procedure and did not observe statistically significant differences between RFA and MOCA recipients.

Effectiveness: Time to Return to Work

Systematic Reviews

A single systematic review (NICE, 2016) reported on time to return to work for MOCA compared to RFA from a single nonrandomized comparative study. Recipients of MOCA were able to return to work a day earlier than RFA recipients (MOCA: 1 day [interquartile range 1 to 2 days] vs. RFA: 2 days [interquartile range 2 to 7 days]; $p = .02$)

Individual Studies

Lane et al. (2017) reported on time to return to work post-procedure and did not observe statistically significant differences between RFA and MOCA recipients.

Harms: Overall Complications

Systematic Reviews

A single systematic review (NICE, 2016) reported on overall complications for MOCA compared to RFA from a single nonrandomized comparative study. There was no statistically significant difference in complications between MOCA and RFA recipients.

Individual Studies

As reported in Lane et al. (2017), overall complications were not statistically significantly different between MOCA and RFA recipients.

Harms: Individual Complications

Systematic Reviews

Two systematic reviews (NICE, 2016; Witte et al., 2017b) reported on individual harms; the former reported comparative data (MOCA vs. RFA) and the latter reported harms only for MOCA recipients. Although there were no statistically significant differences between MOCA and RFA recipients, MOCA was generally found to have lower complications.

Individual Studies

Complications in Lane et al. (2017) included five cases of phlebitis (three MOCA; two RFA) and two deep vein thromboses (one in each arm).

Cost-Effectiveness

Center researchers did not identify any reports on cost or cost-effectiveness for MOCA.

Clinical Practice Guidelines

Center researchers identified one clinical practice guideline that addressed the use of MOCA for the treatment of venous leg insufficiency (NICE, 2016). Center researchers rated the guideline as having poor methodological quality based on absence of information on how the available evidence was used to develop the recommendation. Table 3 provides a summary of guideline recommendations for MOCA. The strength of underlying evidence noted in the table for guideline recommendations is an assessment by the guideline authors, not Center researchers.

The NICE (2016) guideline authors recommended use of MOCA for the treatment of varicose veins, although they noted that longer-term follow-up data are needed. However, this recommendation is based primarily on the Lane et al. (2017) RCT, which has significant

methodological limitations that are not addressed nor incorporated into the language of the NICE (2016) recommendation statement.

Table 3. Summary of Clinical Practice Guidelines’ Recommendations for MOCA

Citation, Methodological Quality†	Recommendation (Evidence Rating*)
National Institute for Health and Care Excellence (2016) Poor	“Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins appears adequate to support the use of this procedure provided that standard arrangements are in place for consent, audit and clinical governance. Clinicians are encouraged to collect longer-term follow-up data.”

Notes. † Determined by Center researchers. *Determined by guideline authors.

Payer Policies

Center researchers searched for policies on the coverage of MOCA from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians’ Health Plan, CMS, Cigna, EmblemHealth, Empire Blue Cross Blue Shield (BCBS), Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, and WA). Table 4 provides a comparison of identified coverage criteria for all payers searched.

Medicare

Center researchers did not identify any national or local coverage determinations for the use of MOCA. However, CPT codes 36473 and 36474 are listed under the Medicare fee schedule, with national and local New York State rates listed for each code. Table 4 outlines the national and local New York State allowable payment amounts.

Private Payers

Eight of the ten private payers searched do not cover the use of MOCA and consider the procedure to be investigational, experimental, and/or unproven (Aetna, Anthem, Blue Shield of Northeastern New York, Cigna, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare). EmblemHealth includes codes 36473 and 36474 in its applicable procedures codes for the treatment of varicose veins, but does not provide any detailed coverage criteria for mechanochemical venous ablation (EmblemHealth, 2017). No coverage policy was identified for Capital District Physicians’ Health Plan.

State Medicaid Agencies

Center researchers did not identify any coverage criteria for the use of MOCA from the search of state Medicaid agency policies. However, several of the state Medicaid agencies searched cover CPT codes 36473 and 36474 because the codes are either listed in a fee schedule or the billing

details for the code are discussed in a provider manual. For example, Medi-Cal (California Medicaid) requires providers to submit a treatment authorization request for CPT codes 36473 and 36474 before performing the procedure in an inpatient or outpatient setting. The codes, however, are not listed in the Medi-Cal fee schedules. Washington Medicaid requires prior authorization for CPT codes 36473 and 36474 as noted in the fee schedule, but the codes are not discussed in the corresponding provider manual.

Other states (MA, NJ, OR, TX, WA) list CPT codes 36473 and 36474 in fee schedules, but do not offer any coverage criteria in the respective provider manuals. Three states (FL, PA, NY) do not provide coverage criteria for CPT codes 36473 and 36474 in the respective provider manuals, nor are the CPT codes listed in the respective fee schedules.

Table 4. Mechanochemical Venous Ablation Coverage Policies

Payer	Coverage Criteria
Medicare	
<i>Center researchers did not identify any national or local coverage determinations on mechanochemical venous ablation.</i>	
<u>Reimbursement</u>	
National Payment Amount	
<ul style="list-style-type: none"> • 36473: \$1,522.40 (non-facility), \$179.80 (facility) • 36474: \$278.86 (non-facility), \$90.08 (facility) 	
Manhattan	
<ul style="list-style-type: none"> • 36473: \$1,782.34 (non-facility), \$206.13 (facility) • 36474: \$324.90 (non-facility), \$103.28 (facility) 	
New York City suburbs/Long Island, NY	
<ul style="list-style-type: none"> • 36473: \$1,836.66 (non-facility), \$216.14(facility) • 36474: \$336.14 (non-facility), \$108.29 (facility) 	
Poughkeepsie, NY/Northern New York City suburbs	
<ul style="list-style-type: none"> • 36473: \$1,631.17 (non-facility), \$191.91 (facility) • 36474: \$298.51 (non-facility), \$96.15 (facility) 	
Rest of New York State	
<ul style="list-style-type: none"> • 36473: \$1,444.34 (non-facility), \$171.56 (facility) • 36474: \$264.91 (non-facility), \$85.95 (facility) 	
Queens	
<ul style="list-style-type: none"> • 36473: \$1,827.40 (non-facility), \$216.29 (facility) • 36474: \$334.89 (non-facility), \$108.36 (facility) 	
Private Payers	
<u>Aetna</u>	Not covered for the treatment of varicose veins.

(last review 8/2017)	
Anthem (last review 5/2017)	Considered investigational and not medically necessary.
Blue Shield of Northeastern New York (last review 5/2017)	Considered investigational.
Capital District Physicians' Health Plan	<i>No coverage criteria identified.</i>
Cigna (last review 11/2016)	Considered experimental, investigational, or unproven.
EmblemHealth (last review 3/2017)	<i>Codes 36473 and 36474 are listed as applicable procedure codes in the coverage policy on varicose vein treatment, but coverage criteria are not discussed.</i>
Empire BCBS (last review 5/2017)	Considered investigational and not medically necessary.
Excellus BCBS (last review 5/2017)	Considered investigational and not medically proven to be effective.
Tufts Health Plan (effective 7/2017)	Considered investigational.
UnitedHealthcare (effective 7/1/2017)	Considered unproven and not medically necessary for treating venous reflux.
State Medicaid	
California (effective 9/2017)	Requires treatment authorization request for the primary surgeon or provider, whether performed on an inpatient or outpatient basis. Assistant surgeons not reimbursable for 36473 and 63474. Reimbursement: 36473 and 36474 not listed.
Florida	<i>No coverage policy identified.</i> Reimbursement: 36473 and 36474 not listed.
Massachusetts (effective 8/2017)	<i>No coverage criteria identified.</i> Reimbursement: 36473: \$1,182.77 (non-facility), \$1,128.67 (facility) 36474: \$212.69 (non-facility), \$64.48 (facility).
New Jersey (effective 1/2017)	<i>No coverage criteria identified.</i> Reimbursement: 36473: \$848.27 (specialist), \$721.03 (non-specialist) 36474: \$153.06 (specialist), \$130.10 (non-specialist).
New York	<i>No coverage policy identified.</i> Reimbursement: 36473 and 36474 not listed.
Oregon	<i>No coverage criteria identified.</i>

<i>(effective 9/2017)</i>	Reimbursement : 36473: \$1,051.82 (non-facility), \$123.40 (facility) 36474: \$192.36 (non-facility), \$61.82 (facility).
Pennsylvania	<i>No coverage criteria identified.</i> Reimbursement : 36473 and 36474 not listed.
Texas <i>(effective 1/2017)</i>	<i>No coverage criteria identified.</i> Reimbursement : 36473: \$1,190.61 (0 to 20 years), \$1,133.91 (21+ years) 36474: \$218.08 (0 to 20 years), \$207.70 (21+ years).
Washington <i>(effective)</i>	<i>No coverage criteria identified.</i> Reimbursement : 36473: \$919.95 (non-facility), \$102.06 (facility), prior authorization required, assistant surgeon not reimbursable. 36474: \$166.15 (non-facility), \$80.07 (facility), prior authorization required, assistant surgeon not reimbursable.

Abbreviations. BCBS: Blue Cross Blue Shield; CPT: Current Procedural Terminology.

Discussion

MOCA is a newer technique to treat varicose veins that uses a catheter inserted into the varicose vein after a small amount of local anesthesia is used to numb the insertion site. A wire is inserted through the catheter to irritate the wall of the vein while a chemical is infused to achieve vein occlusion. Procedure-related pain appears to be lower for MOCA recipients compared to RFA, and occlusion rates at six months are similar. The available data on MOCA are from studies with significant limitations that could introduce bias, and subsequent studies could find different results. There is a lack of long-term effectiveness data.

Center researchers identified a single poor methodological quality guideline that recommended use of MOCA for the treatment of varicose veins, but the authors stated that additional long-term follow-up data are needed. This recommendation is based on the single available poor methodological quality RCT comparing MOCA to RFA.

Eight of the ten of private payers searched do not cover MOCA. Medicare and five of the nine state Medicaid agencies searched include pricing for the MOCA-related CPT codes, but do not offer additional coverage criteria. Medicaid agencies in Florida, New York, and Pennsylvania do not include the CPT codes for MOCA in their fee schedules, nor do they outline coverage criteria for MOCA in their respective provider manuals.

Strength of Evidence

The Center uses the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group approach to enhance consistency in grading the strength of evidence. RCTs are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength rating is downgraded depending

on the severity of the bias, based on limitations including study risk of bias; inconsistency (i.e., differences between study findings indicated by statistical or clinical heterogeneity); indirectness (i.e., limited generalizability of the findings from the study sample to another population); imprecision (i.e., wide confidence intervals); and high probability of reporting bias, also known as publication bias. The rating can be increased from low for evidence from observational studies if there is a strong association,³ a very strong association,⁴ or a dose-response gradient. The rating is also increased if all plausible confounders have reduced the estimate (Schünemann, Brozek, Guyatt, & Oxman, 2014). Table 5 provides an overview of the strength of evidence outcome, and associated rationale for the strength of evidence rating.

Table 5. Strength of Evidence for MOCA: Effectiveness, Harms, and Cost-Effectiveness

Outcome	Strength of Evidence Assessment	Rationale
Effectiveness		
Quality of life (AVVQ) MOCA appears to have similar QoL as RFA	Very Low	Evidence derives from a fair methodological quality systematic review (using data from a single nonrandomized comparative study) and a single poor-quality RCT. Follow-up limited to 6 months at most. <ul style="list-style-type: none"> • Downgraded for risk of bias and imprecision
Symptom severity (VCSS) MOCA appears to have similar effect on symptom severity as RFA	Very Low	Evidence derives from a single fair methodological quality systematic review (using data from a single nonrandomized comparative study) and a single poor-quality RCT. Follow-up limited to 6 weeks. There is no comparative data to other procedures or lifestyle changes. <ul style="list-style-type: none"> • Downgraded for risk of bias and indirectness
Occlusion rates MOCA appears to have similar occlusion rates to RFA at ≥6 months	Low	Evidence derives from a fair methodological quality systematic review (of case series data) and a poor-quality RCT with follow up of 12 months. <ul style="list-style-type: none"> • Downgraded for risk of bias and indirectness
Return to work MOCA recipients may return to work 1 day earlier than RFA	Very Low	Evidence derives from a fair methodological quality systematic review (using data from a single

³ Significant relative risk of >2 or <0.5 with no plausible confounders in two or more observational studies.

⁴ Significant relative risk of >5 or <0.2 based on direct evidence with no major threats to validity.

Outcome	Strength of Evidence Assessment	Rationale
recipients		nonrandomized comparative study) and a single poor-quality RCT. <ul style="list-style-type: none"> Downgraded for risk of bias and imprecision
Harms		
Complications MOCA appears to have similar or fewer complications than RFA	Low	Evidence derives from one fair and one poor methodological quality systematic review. Complications are rare, not statistically different between RFA and MOCA, but small sample sizes, short follow-up periods, and industry funding may introduce bias. <ul style="list-style-type: none"> Downgraded for risk of bias two levels
Cost or Cost-Effectiveness		
The current search did not identify any evidence on costs or cost-effectiveness.		

Abbreviations. AVVQ: Aberdeen Varicose Vein Questionnaire; MOCA: mechanochemical ablation; QoL: quality of life; RCT: randomized controlled trial; RFA: radiofrequency ablation; VCSS: Venous Clinical Severity Score.

References

- Aber, A., Poku, E., Phillips, P., Essat, M., Buckley Woods, H., Palfreyman, S., . . . Michaels, J. (2017). Systematic review of patient-reported outcome measures in patients with varicose veins. *British Journal of Surgery*, *104*(11), 1424-1432. doi: 10.1002/bjs.10639
- American College of Phlebology. (n.d.). *What is CEAP*. Retrieved from <http://www.phlebology.org/patient-information/online-vein-self-assessment-vein/what-is-ceap>
- American Psychological Association. (2017). *PsycINFO*. Retrieved from <http://www.apa.org/pubs/databases/psycinfo/?tab=3>
- Boersma, D., Kornmann, V. N., van Eekeren, R. R., Tromp, E., Unlu, C., Reijnen, M. M., & de Vries, J. P. (2016). Treatment modalities for small saphenous vein insufficiency: Systematic review and meta-analysis. *Journal of Endovascular Therapy*, *23*(1), 199-211. doi: <https://dx.doi.org/10.1177/1526602815616375>
- Bootun, R., Lane, T. R., Dharmarajah, B., Lim, C. S., Najem, M., Renton, S., . . . Davies, A. H. (2016). Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre VenefitTM versus ClariVein for varicose veins trial. *Phlebology*, *31*(1), 61-65. doi: <https://dx.doi.org/10.1177/0268355514551085>
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., . . . Zitzelsberger, L. (2010). AGREE II: Advancing guideline development, reporting and evaluation in health care. *Canadian Medical Association Journal*, *182*(18), E839-E842. doi: 10.1503/cmaj.090449
- Campbell Collaboration. (2015). Campbell Collaboration systematic reviews: Policies and guidelines. *Campbell Systematic Reviews, Supplement 1*. doi: 10.4073/csrs.2015.1
- Deijen, C. L., Schreve, M. A., Bosma, J., de Nie, A. J., Leijdekkers, V. J., van den Akker, P. J., & Vahl, A. (2016). ClariVein mechanochemical ablation of the great and small saphenous vein: Early treatment outcomes of two hospitals. *Phlebology*, *31*(3), 192-197. doi: <https://dx.doi.org/10.1177/0268355515600573>
- Eklof, B., Perrin, M., Delis, K. T., Rutherford, R. B., & Gloviczki, P. (2009). Updated terminology of chronic venous disorders: The VEIN-TERM transatlantic interdisciplinary consensus document. *Journal of Vascular Surgery*, *49*(2), 498-501. doi: <https://doi.org/10.1016/j.jvs.2008.09.014>

- Elias, S., & Raines, J. K. (2012). Mechanochemical tumescentless endovenous ablation: Final results of the initial clinical trial. *Phlebology*, 27(2), 67-72. doi: 10.1258/phleb.2011.010100
- EmblemHealth. (2017). *Varicose vein treatment*. Retrieved from https://www.emblemhealth.com/~media/Files/PDF/med_guidelines/MG_Varicose_Vein_b.pdf.
- Food and Drug Administration. (2008). *ClariVein infusion catheter 510(k) summary statement*. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf7/K071468.pdf.
- Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care & Research*, 63(S11), S240-S252. doi: 10.1002/acr.20543
- Higgins, J. P. T., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions*. <http://handbook.cochrane.org/>.
- Institute for Quality and Efficiency in Health Care. (2008). *Varicose veins: Overview*. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072431/>
- Jones, R. H., & Carek, P. J. (2008). Management of varicose veins. *American Family Physician*, 78(11), 1289-1294.
- Kim, P. S., Bishawi, M., Draughn, D., Boter, M., Gould, C., Koziarski, J., . . . Hamilton, R. (2017). Mechanochemical ablation for symptomatic great saphenous vein reflux: A two-year follow-up. *Phlebology*, 32(1), 43-48. doi: <https://dx.doi.org/10.1177/0268355515627260>
- Kugler, N. W., & Brown, K. R. (2017). An update on the currently available nonthermal ablative options in the management of superficial venous disease. *Journal of Vascular Surgery*, 5(3), 422-429. doi: <https://dx.doi.org/10.1016/j.jvsv.2017.01.014>
- Lam, Y. L., Toonder, I. M., & Wittens, C. H. (2016). Clarivein mechano-chemical ablation an interim analysis of a randomized controlled trial dose-finding study. *Phlebology*, 31(3), 170-176. doi: <https://dx.doi.org/10.1177/0268355515599692>
- Lane, T., Bootun, R., Dharmarajah, B., Lim, C. S., Najem, M., Renton, S., . . . Davies, A. H. (2017). 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*, 32(2), 89-98. doi: <https://dx.doi.org/10.1177/0268355516651026>
- Mayo Clinic. (2017). *Varicose veins--overview*. Retrieved from <http://www.mayoclinic.org/diseases-conditions/varicose-veins/home/ovc-20178078>
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6(7), e1000097. doi: 10.1371/journal.pmed.1000097
- National Institute for Health and Care Excellence. (2014). *Developing NICE guidelines: The manual*. Retrieved from <https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf>
- National Institute for Health and Care Excellence. (2016). *Interventional procedure overview of endovenous mechanochemical ablation for varicose veins*. London: NICE. Retrieved from <https://www.nice.org.uk/guidance/ipg557/documents/overview>.
- Ovid. (2017). *Ovid MEDLINE*. Retrieved from <http://www.ovid.com/site/catalog/databases/901.jsp#horizontalTab2>
- Proebstle, T., & van den Bos, R. (2017). Endovenous ablation of refluxing saphenous and perforating veins. *Vasa*, 46(3), 159-166. doi: <https://dx.doi.org/10.1024/0301-1526/a000610>
- Schünemann, H., Brozek, J., Guyatt, G., & Oxman, A. (2014). *GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013*. Retrieved from <http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>
- Scottish Intercollegiate Guidelines Network. (2015a). *Methodology checklist 1: Systematic reviews and meta-analyses*. Retrieved from <http://www.sign.ac.uk/checklists-and-notes.html>
- Scottish Intercollegiate Guidelines Network. (2015b). *Methodology checklist 2: Randomised controlled trials*. Retrieved from <http://www.sign.ac.uk/checklists-and-notes.html>
- Tang, T. Y., Kam, J. W., & Gaunt, M. E. (2017). ClariVein--Early results from a large single-centre series of mechanochemical endovenous ablation for varicose veins. *Phlebology*, 32(1), 6-12. doi: <https://dx.doi.org/10.1177/0268355516630154>

Vasquez, M. A., & Munschauer, C. E. (2008). Venous Clinical Severity Score and quality-of-life assessment tools: Application to vein practice. *Phlebology*, 23(6), 259-275. doi: 10.1258/phleb.2008.008018

Washington Health Technology Assessment Program. (2017). *Selected treatments for varicose veins*. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from <https://www.hca.wa.gov/assets/program/varicose-veins-final-rpt-20170420.pdf>.

Witte, M. E., Holewijn, S., van Eekeren, R. R., de Vries, J. P., Zeebregts, C. J., & Reijnen, M. M. (2017a). Midterm outcome of mechanochemical endovenous ablation for the treatment of great saphenous vein insufficiency. *Journal of Endovascular Therapy*, 24(1), 149-155. doi: <https://dx.doi.org/10.1177/1526602816674455>

Witte, M. E., Zeebregts, C. J., de Borst, G. J., Reijnen, M., & Boersma, D. (2017b). Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review. *Phlebology*, 268355517702068. doi: 10.1177/0268355517702068

Appendix A. Pain Scales and Classifications of Venous Insufficiency

Clinical, Etiology, Anatomy, Pathophysiology (CEAP)

The CEAP is a classification system designed to establish standard terminology to discuss and classify venous disorders (American College of Phlebology, n.d.). The clinical section (C), outlined in Table A1, is the most commonly used portion of the CEAP system (American College of Phlebology, n.d.).

Table A1. CEAP Clinical Section

Clinical Classification	Description
C0	No sign of venous disease
C1	Spider or reticular veins
C2	Varicose veins
C3	Presence of edema of the ankle
C4 (a and b)	Pigmentation (darkening) of the skin, eczema (redness, itching), lipodermatosclerosis (hardening of the soft tissue), and atrophie blanche (whitish skin area)
C5	Healed venous ulcer present
C6	Active open venous ulcer

Source. Adapted from American College of Phlebology (n.d.).

Aberdeen Varicose Vein Questionnaire (AVVQ)

The [AVVQ](#) includes 13 questions that evaluate pain, use of pain medication, ankle edema, ulcers, itching, rash or eczema, compression therapy use, effect of varicose veins on daily activities, and cosmetic effect of varicose veins (Vasquez & Munschauer, 2008). The questionnaire is scored from zero (no effect from varicose veins) to 100 (severe effect of varicose veins) (Vasquez & Munschauer, 2008). The AVVQ is designed to be conducted at baseline, and at six-weeks, six-months, and 12-months follow-up.

Venous Clinical Severity Score (VCSS)

The VCSS is based on elements of the CEAP classification and includes three components: venous disability score, venous segmental disease score, and venous clinical severity score (Vasquez & Munschauer, 2008). The venous disability score uses a scale of zero to three and evaluates the "ability to work an eight-hour day with or without a 'support device'" (Vasquez & Munschauer, 2008, p. 266). The venous segmental disease score is based on the anatomical and pathophysiological components of the CEAP classification and typically uses duplex Doppler or phlebography to determine the grade of venous reflux or obstruction (Vasquez & Munschauer,

2008). The venous clinical severity score uses a severity score of zero to 3 and evaluates skin changes, inflammation and induration, and ulcers (Vasquez & Munschauer, 2008).

Visual Analog Scale (VAS)

The VAS for pain uses a one dimensional measurement for pain intensity (Hawker, Mian, Kendzerska, & French, 2011). The pain VAS typically uses a 10 cm line (100 mm) that is marked on each end with a symptom extreme (e.g., no pain, worst pain imaginable) (Hawker et al., 2011). Scores range from 0 mm (no pain) to 100 mm (worst pain imaginable) (Hawker et al., 2011). Suggested cutoffs for pain VAS scores include no pain (0 to 4 mm), mild pain (5 to 44 mm), moderate pain (45 to 74 mm), and severe pain (75 to 100 mm) (Hawker et al., 2011).

Appendix B. Methods

Search Strategies

Evidence

A full search of the Center’s core clinical evidence primary sources was conducted to identify systematic reviews, meta-analyses, and technology assessments using the search terms *mechanochemical* and *endochemical*. Searches of core sources were limited to citations published after 2006. Center researchers also searched the Ovid MEDLINE database for relevant systematic reviews and meta-analyses, technology assessments, individual studies, and cost-effectiveness studies published after 2015.

The following core sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- BMJ – Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE)
- PubMed Health
- Tufts Cost-Effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

Clinical Practice Guidelines

Center researchers conducted a full search of Center clinical practice guidelines primary sources to identify clinical practice guidelines using the terms *mechanochemical* and *endochemical*. Searches were limited to citations published within the last five years. Center researchers included guidelines from governmental bodies and professional associations; guidelines from single clinical institutions (e.g., a single hospital or clinic) were not included.

The guideline sources included the following:

- American College of Phlebology
- Australian Government National Health and Medical Research Council (NHMRC)
- National Guidelines Clearinghouse
- National Institute for Health and Care Excellence (NICE)
- New Zealand Guidelines Group

Scottish Intercollegiate Guidelines Network (SIGN)

Veterans Administration/Department of Defense (VA/DOD)

World Health Organization (WHO)

Center researchers searched Google 10 pages deep using the terms *mechanochemical* and *guideline or position or practice or statement*.

Coverage Policies

Center researchers searched for policies on the coverage of MOCA from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians' Health Plan, CMS, Cigna, Emblem Health, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, and WA).

Ovid MEDLINE

The Ovid MEDLINE search strategy was developed for broad inclusion of relevant systematic reviews and individual studies. Individual studies published after the search dates of the included systematic review or studies that were eligible and not included in the systematic review were included to update the systematic review.

Database: Ovid MEDLINE <1946 to July Week 1 2017>, Ovid MEDLINE In-Process & Other Non-Indexed Citations <September 13, 2017>

Search Strategy:

- 1 exp venous insufficiency/
- 2 ((venous or vein\$) adj4 (incomp\$ or insuffic\$)).tw.
- 3 ((venous or vein\$) adj4 ulcer\$).tw.
- 4 telangiectasis/
- 5 telangiect\$.tw.
- 6 ((reticular or thread or spider) adj4 (vein\$ or venous)).tw.
- 7 1 or 2 or 3 or 4 or 5 or 6
- 8 exp lower extremity/
- 9 (lower limb\$ or lower extremit\$ or leg\$ or calf or valves or thigh\$ or membrum inferius).tw.
- 10 8 or 9
- 11 7 and 10
- 12 exp varicose veins/
- 13 (varicos\$ adj4 vein\$).tw.
- 14 (varix or varices or microvaricosity or phlebarteriectasia or phlebectas\$ or prevaricos\$ or vein ectasia or venectasia).tw.
- 15 Saphenous Vein/
- 16 ((saphenous or perforator) adj4 (vein\$ or vena or incomp\$ or insuffic\$)).tw.

- 17 GSV.tw.
- 18 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19 clarivein.tw.
- 20 MOCA.tw.
- 21 ((mechanochemical or mechano-chemical or mechanical) adj4 ablat\$.tw.
- 22 ((non-thermal or nonthermal or "non thermal") adj4 ablat\$.tw.
- 23 (infus\$ adj4 catheter\$.tw.
- 24 ((damag\$ or disrupt\$ or disturb\$ or destroy\$ or break\$ or destruct\$) adj4 (endothelium or endothelial or lining)).tw.
- 25 (rotat\$ adj4 (wire\$ or tip\$)).tw.
- 26 tumescentless.tw.
- 27 ((spasm\$ adj2 vein\$) or venospasm).tw.
- 28 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
- 29 18 and 28
- 30 animals/ not humans/
- 31 29 not 30
- 32 limit 31 to english language
- 33 limit 32 to yr="2016 -Current"

Study Inclusion/Exclusion Criteria

Two Center researchers independently reviewed the results from the Center core sources and Ovid MEDLINE database searches at each stage of review (e.g., title and abstract, full text). Any study that was identified by at least one researcher as potentially meeting inclusion criteria was advanced to the next review level. All excluded studies were determined by two Center researchers as not meeting the predetermined inclusion criteria. Any disagreement between study reviewers regarding the inclusion of a study was arbitrated by a third Center researcher. Center researchers excluded studies that were not systematic reviews, meta-analyses, technology assessments, or individual studies (as applicable by topic); that were published before 2007; were published in a language other than English; or did not meet the specific inclusion/exclusion criteria outlined below.

Inclusion Criteria

Population: Individuals with symptomatic lower extremity chronic venous disease

Intervention: Mechanochemical ablation

Comparators: Conservative therapy (e.g., compression, leg elevation); other endovenous ablation therapies (e.g., laser, radiofrequency); sclerotherapy; surgery (e.g., ligation/stripping, phlebectomy)

Outcomes: Symptom resolution, quality of life, function, time to complete healing, incidence of repeat procedure or other procedures, adverse events, economic outcomes (e.g., cost, cost-effectiveness)

Key Questions

1. What is the comparative effectiveness of mechanochemical ablation to other treatment modalities for chronic venous insufficiency? Does effectiveness vary according to:
 - a. Clinical, etiology, anatomy, pathophysiology (CEAP) scale zero to six
 - b. Presence of reflux or obstruction
 - c. Anatomic location
 - d. Step therapy
2. How do the adverse events from mechanochemical venous ablation compare with other treatment modalities for chronic venous insufficiency?
3. What is the cost and cost-effectiveness of mechanochemical ablation for chronic venous insufficiency compared to other treatment modalities?
4. What are the clinical practice guidelines on the use of mechanochemical ablation for chronic venous insufficiency?
5. What are federal, state Medicaid, and private payer coverage policies for the use of mechanochemical ablation?

Exclusion Criteria

Study exclusion criteria included the following:

- Animal and in-vitro studies
- Studies only reporting on laboratory biological markers, historical findings, technical success without follow-up, and procedure time
- Case series that did not report on harms
- Case reports, letters, editorials, comments
- Duplicate information from a research study published in more than one source (only the highest quality, most recent publication with outcome of interest was included)
- Systematic reviews that included only studies that were summarized by more comprehensive systematic reviews or systematic reviews of higher quality and/or that were more recently published
- Studies identified that were included in a summarized systematic review or technology assessment

Quality Assessment

Center researchers assessed the methodological quality of the included studies using standard instruments developed and adapted by the Center that are modifications of the systems in use by the Campbell Collaboration, Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) (Brouwers et al., 2010; Campbell Collaboration, 2015; Higgins & Green, 2011; Moher, Liberati, Tetzlaff, & Altman, 2009; NICE, 2014; SIGN, 2015a; SIGN, 2015b) Two Center researchers independently rated all studies. In cases where there was not agreement about the quality of a study, consensus was reached through discussion.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine whether a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Appendix C. Articles Selected for Full-Text Review Exclusion Rationale

Citation	Exclusion Rationale
Boersma et al. (2016)	Exclude: Superseded by newer, more comprehensive SR
Bootun et al. (2016)	Exclude: Updated by Witte et al. (2017b)
Deijen et al. (2016)	Exclude: Included in Witte et al. (2017b)
Kim et al. (2017)	Exclude: Included in Witte et al. (2017b)
Kugler and Brown (2017)	Exclude: Superseded by newer, more comprehensive SR
Proebstle and van den Bos (2017)	Exclude: Study design (narrative review)
Tang et al. (2017)	Exclude: Included in Witte et al. (2017b)
Washington Health Technology Assessment Program (2017)	Exclude: Intervention (does not evaluate MOCA)
Witte et al. (2017a)	Exclude: Included in Witte et al. (2017b)

Abbreviations. MOCA: mechanochemical ablation; SR: systematic review.

Appendix D. List of Trials Registered on Clinicaltrials.gov

Trial Name ClinicalTrials.gov Identifier	Status	Notes
Mechanochemical Endovenous Ablation (MOCA) Versus Radiofrequency Ablation (RFA) in the Treatment of Primary Great Saphenous Varicose Veins: a Multicentre Randomized Trial NCT01936168	Active, not recruiting	Device: Mechanochemical Endovenous Ablation Procedure: Radiofrequency Ablation Completion Date: December 2020
Registry of the Treatment of Primary Insufficiency of the Great Saphenous Vein With a Diameter \geq 12 mm, Antero-lateral Branches, or Great Saphenous Vein Insufficiency Below the Knee With Mechanochemical Endovenous Ablation (MOCA) NCT02345018	Active, not recruiting	Procedure: Mechanochemical Ablation Completion Date: December 2020
Mechanochemical Endovenous Ablation of Great Saphenous Vein Incompetence Using the ClariVein Device: A Prospective Study NCT01459263	Active, not recruiting	Device: ClariVein Completion Date: April 2017
A Randomised Clinical Trial Comparing Standard Cannula Delivered Foam Sclerotherapy, Catheter Directed Foam Sclerotherapy and ClariVein Mechanochemical Ablation in the Management of Superficial Venous Insufficiency NCT02010437	Withdrawn	Drug: Sodium Tetradecyl Sulphate Comparators: Form Sclerotherapy, Catheter-directed foam sclerotherapy, ClariVein Completion Date: April 2015
A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency NCT02627846	Recruiting	Device: Endovenous Laser Ablation Device: Mechanochemical Ablation Drug: Lidocaine with 1:200,000 epinephrine solution Drug: Sodium Bicarbonate Drug: Sodium Tetradecyl Sulphate Completion Date: September 2030

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