

Medical Policy



Title: **Diagnosis and Treatment of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis**

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With multiple sclerosis	Interventions of interest are: • Ultrasound with or without magnetic resonance imaging to diagnose chronic cerebrospinal venous insufficiency	Comparators of interest are: • Standard care without diagnosis of chronic cerebrospinal venous insufficiency	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures
Individuals: • With multiple sclerosis and chronic cerebrospinal venous insufficiency	Interventions of interest are: • Treatment of chronic cerebrospinal venous insufficiency with percutaneous venoplasty	Comparators of interest are: • Standard care without percutaneous venoplasty	Relevant outcomes include: • Overall survival • Symptoms • Quality of life • Treatment-related morbidity

DESCRIPTION

Chronic cerebrospinal venous insufficiency (CCSVI) may be associated with multiple sclerosis (MS), although this is controversial and an active area of research. Correction of CCSVI in patients with MS has been attempted using percutaneous venoplasty. The intent of this procedure is to relieve MS symptoms by improving venous drainage of the central nervous system.

Objective

The objectives of this evidence review are to evaluate whether chronic cerebrospinal venous insufficiency (CCSVI) is associated with multiple sclerosis (MS), whether ultrasound with or without magnetic resonance imaging can accurately diagnose CCSVI in MS patients, and whether percutaneous venoplasty in patients with MS diagnosed with CCSVI can improve the net health outcome.

Background

Multiple sclerosis (MS) is generally considered a chronic inflammatory demyelinating disease of the central nervous system (brain, spinal cord, optic nerve) believed to be triggered by an autoimmune response to myelin. However, in part due to the periventricular predilection of the lesions of MS, vascular etiologies (chronic cerebrospinal venous insufficiency [CCSVI]) have also been considered. The core foundation of this vascular theory is that venous drainage from the brain is abnormal due to outflow obstruction in the draining jugular vein and/or azygos veins. This abnormal venous drainage, which is characterized by special ultrasound criteria, is said to cause intracerebral flow disturbance or outflow problems that lead to periventricular deposits. In the CCSVI theory, these deposits have a similarity to the iron deposits seen around the veins in the legs in patients with chronic deep vein thrombosis. Balloon dilatation, with or without stenting, has been proposed as a means to treat the outflow problems, thereby alleviating CCSVI and MS complaints.

The following 5 criteria were defined by Zamboni et al in 2009 as features of CCSVI.¹ To make the diagnosis of CCSVI, at least 2 of the 5 criteria need to be present:

1. Reflux constantly present (for a duration >0.8 seconds) in the supine and upright positions at the level of an internal jugular or vertebral vein. This parameter was evaluated during a short breath-hold following normal breathing and not under Valsalva maneuver.
2. Reflux at the level of veins of the deep cerebral system (for a duration >0.5 seconds). This was evaluated with the patient in the sitting and supine positions, and venous flow was enhanced by inviting the patient to breath in.
3. Stenosis (<0.3 cm), valve abnormalities, and septa on B-mode imaging.
4. Absence of flow at the level of the internal jugular or vertebral vein, despite numerous deep inspirations.
5. No increase in the diameter of the internal jugular vein when changing from an upright to a supine position (lack of change in pressure).

In 2014, the International Society for Neurovascular Disease published modifications to the Zamboni Doppler ultrasound protocol and described protocols for additional imaging using magnetic resonance and intravascular ultrasound to supplement Doppler ultrasound.² The revised ultrasound criteria, originally proposed in 2011, are:

1. Reflux present in the internal jugular or vertebral veins:
 - a. Bidirectional flow in 1 or both internal jugular veins in both positions (supine or upright) or bidirectional flow in 1 position with absence of flow in the other position;
 - b. Reversal of flow or bidirectional flow in 1 or both venous veins in both positions.
2. Internal jugular vein stenosis:
 - a. Reduction of proximal internal jugular vein cross-sectional area in the supine position to no more than 0.3 cm², which does not increase with Valsalva maneuver.
 - b. Structural abnormalities.
3. Absence of detectable flow in the internal jugular veins or venous veins despite numerous deep inspirations and bidirectional flow detected in the other position on the same side.
4. The cross-sectional area of the internal jugular vein is greater in the seated than supine position or is similar in the 2 positions.
5. Bidirectional flow in the intracranial vein and sinuses (recommended as an additional criterion).

Regulatory Status

Endovascular correction of chronic cerebrospinal venous insufficiency is a surgical procedure and as such is not subject to regulation by the U.S. Food and Drug Administration.

POLICY

The identification and subsequent treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis is considered **experimental / investigational**.

RATIONALE

This evidence review was updated with searches of the MEDLINE database. Most recently, the literature was reviewed through October 4, 2016. The following is a summary of the key literature.

Diagnosis of Chronic Cerebrospinal Venous Insufficiency

In 2009, Zamboni et al used 5 ultrasound criteria (see Background section) to define the condition of chronic cerebrospinal venous insufficiency (CCSVI).¹ In initial research reports, these investigators reported 100% sensitivity and 100% specificity in separating patients with multiple

sclerosis (MS) from controls when applying these criteria.³ Since publication of the Zamboni studies, numerous other research studies have attempted to replicate its findings on the association between CCSVI in MS patients (ie, comparing rates of CCSVI in MS patients and healthy controls and/or patients with other neurologic diagnoses).

Systematic Reviews

In 2014, a meta-analysis on the association between CCSVI and MS was published by Tsvigoulis et al.⁴ Nineteen studies (1250 MS patients, 899 healthy controls) were included in the meta-analysis. CCSVI was associated with MS in the pooled analysis (odds ratio [OR], 8.35; 95% confidence interval [CI], 3.44 to 20.31; $p < 0.001$). Heterogeneity across studies was considerable ($I^2 = 80.1\%$). In additional sensitivity analyses, the odds ratio associating CCSVI and MS decreased. In the most conservative sensitivity analysis, which excluded 8 studies (studies by Zamboni or associated groups and studies conducted in Italy or by advocates of endovascular procedures for CCSVI), MS was not associated with CCSVI (OR=1.35; 95% CI, 0.62 to 2.93; $p = 0.453$). Additionally, heterogeneity was not found ($I^2 = 0\%$).

Zwischenberger et al in 2013 reported on a meta-analysis of the association between MS and CCSVI diagnosed by ultrasound.⁵ Thirteen studies (1141 MS patients, 738 healthy controls) were included in the meta-analysis. Initial analysis demonstrated CCSVI was associated with MS (OR=2.57; $p < 0.001$), but heterogeneity was significant ($I^2 = 82.7\%$; $p < 0.001$). In a subsequent analysis of 9 studies with 4 outliers (studies with disproportionately high ORs) removed, the odds ratio decreased, but still associated CCSVI with MS (OR=1.885; $p < 0.001$) and heterogeneity decreased ($I^2 = 18\%$; $p = 0.279$).

A systematic review of the association between CCSVI and MS was published in 2011 by Laupacis et al.⁶ It included 8 studies that used ultrasound to diagnose CCSVI by Zamboni criteria and compared the rate of CCSVI in patients with MS to those without MS. Studies were mostly small, with the median number of patients with MS of 50. A large degree of heterogeneity existed across studies in the rate of CCSVI among MS patients. Two smaller studies reported a rate of 0% for CCSVI (n range, 20-56 patients with MS). In contrast, the original study by Zamboni et al reported a 100% rate of CCSVI in 109 patients with MS. A small study of 25 patients also reported a very high rate of CCSVI at 84% (21/25). No obvious reason was identified for this large discrepancy in CCSVI rates; the authors hypothesized that the most likely reason was variability in ultrasound technique and interpretation. The analysis suggested a significant association between CCSVI and MS in combined analysis, with an odds ratio of 13.5 (95% CI, 2.6 to 71.4). A substantial degree of heterogeneity existed in this measure as well ($I^2 = 89\%$). Several sensitivity analyses showed marked variability of the odds ratio from a low of 3.7 to more than 58,000. However, in all cases the association between CCSVI and MS remained significant.

A 2011 systematic review published that included 4 studies found the rate of CCSVI in MS patients ranged from 7% to 100%, while the rate in non-MS patients ranged from 2% to 36%.⁷ A significant association was detected between MS and CCSVI, but with a high degree of heterogeneity ($I^2 = 96\%$) and an odds ratio for association that varied widely, from approximately 2 to more than 26,000.

Controlled Observational Studies

Observational studies published more recently than the systematic reviews are described next. In 2016, Fox et al published a study with 61 MS patients and 20 non-MS controls (15 healthy

individuals, 5 patients with other neurologic disorders).⁸ Zamboni criteria were used to assess patients. However, investigators used 2 interpretations of the ultrasound data that involved narrow and broad interpretations of criteria 2 and 3. Using the narrow criteria, the incidence of CCSVI (ie, meeting ≥ 2 of 5 criteria) was 21.3% in MS patients and 20.0% in controls ($p=0.99$). Using broad criteria, estimates were 36.1% in MS patients and 40% in controls ($p=0.75$). In addition, there were no significant differences in the proportion of MS and control patients who met any single ultrasound criterion.

A 2016 study by Cardaioli et al included 57 subjects (39 MS patients, 18 healthy individuals).⁹ Study participants were assessed using Zamboni criteria for CCSVI as revised by the International Society for Neurovascular Disease (ISNVD).² Seventeen (43.6%) MS patients and 6 (33.3%) healthy controls met the diagnostic criteria for CCSVI; the difference between groups was not statistically significant ($p=0.4$). In addition, there were no statistically significant differences between MS patients and healthy controls on any single CCSVI criterion.

In 2016, Schrauben et al evaluated 172 subjects (76 MS patients, 53 healthy controls) who were age- and sex-matched to MS patients and 43 patients with other neurologic diseases.¹⁰ Patients were assessed with ultrasound and 4-dimensional (4D) magnetic resonance imaging (MRI) augmented by contrast-enhanced magnetic resonance venography (MRV). Twelve (15.8%) MS patients, 15 (9.3%) patients with other neurologic diseases, and 9 (17.0%) healthy controls met ultrasound criteria for CCSVI. The difference between groups was not statistically significant (p value not reported). Moreover, no 4D MRI parameter differed significantly among groups and contrast-enhanced MRV did not identify significant differences in stenosis scores among groups.

Section Summary: Diagnosis of Chronic Cerebrospinal Venous Insufficiency

The relation between CCSVI and MS remains unclear. Initial reports of excellent discrimination of patients with and without MS using CCSVI ultrasound criteria have not been replicated in subsequent studies. Systematic reviews have generally found a statistically significant association between CCSVI and MS, but a 2014 meta-analysis that excluded studies by Zamboni and associated research groups found no significant association. Moreover, systematic reviews have reported significant heterogeneity among studies. Recent observational studies have not found that Zamboni criteria or updated criteria proposed by the ISNVD can discriminate between patients with and without MS.

Treatment of CCSVI With Percutaneous Venoplasty

Initial interest in percutaneous venoplasty to treat patients with MS and CCSVI came after publication of case series by Zamboni et al. For example, in a pilot series of 65 patients with MS and CCSVI, Zamboni et al reported clinical improvement following catheter-based venoplasty.³ Patients were subdivided by MS clinical course into relapsing-remitting ($n=35$), secondary progressive ($n=20$), and primary progressive ($n=10$) MS, and all patients underwent percutaneous transluminal angioplasty (PTA). Mean follow-up was 18 months. In this study, outpatient endovascular treatment of CCSVI was noted to be feasible, with a minor complication rate. Postoperative venous pressure was significantly lower. The endovascular treatment was noted to improve MS clinical outcome measures, especially in the relapsing-remitting group: the rate of relapse-free patients changed from 27% to 50% postoperatively ($p<0.001$). The Multiple Sclerosis Functional Composite at 1 year improved significantly in relapsing remitting patients ($p<0.008$) but not in primary progressive or secondary progressive. Physical quality of life (QOL) improved significantly in relapsing-remitting ($p<0.01$) and primary progressive ($p<0.03$) patients,

with a positive trend in secondary progressive ($p < 0.08$). The authors concluded that PTA of venous strictures in patients with CCSVI is safe, and especially in patients with relapsing-remitting disease, the clinical course was positively influenced by treatment. The authors also indicated a randomized controlled trial (RCT) is warranted.

In a 2012 Cochrane review, van Zuuren et al found no RCTs on the treatment of CCSVI in MS patients.¹¹ Reviewers concluded the efficacy or safety of PTA for CCSVI treatment in MS patients could not be determined. A 2014 update of this Cochrane review also did not identify any RCTs.¹²

An RCT was published in 2014, after the literature search date cutoff for the Cochrane review. The RCT, by Siddiqui et al, was double-blind, sham-controlled, and evaluated of venous angioplasty in MS patients with CCSVI.¹³ This trial enrolled 9 patients in intervention group and 10 in the sham-controlled group. All patients met the criteria for diagnosis of CCSVI.¹⁴ The primary end points of the trial included safety at 24 hours and 30 days after angioplasty; greater than 75% restoration of venous outflow at 30 days; the presence of new MS lesions; and relapse rate over 6 months. Secondary end points included changes in disability scores, brain volume, cognitive test scores, and QOL measures. All patients tolerated the procedures well; no operative or postoperative complications were identified. One patient in the angioplasty group experienced an episode of symptomatic bradycardia. No significant differences were observed in venous outflow characteristics between the treated and control groups, nor were any significant improvements observed in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients. However, the failure to show a beneficial effect of venous angioplasty on MS activity supports a lack of efficacy for this treatment.

The authors of a 2015 comprehensive literature review of venous angioplasty as treatment for CCSVI in MS concurred, concluding that venous angioplasty has no proven efficacy for treating CCSVI in MS, may exacerbate underlying disease activity, and suggesting that the treatment should no longer be offered, even in clinical trials.¹⁵

Adverse Events

A Food and Drug Administration (FDA) alert issued in May 2012 reported the potential for adverse events following endovascular interventions for MS.¹⁶ Reports of adverse events obtained by FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This alert included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption because of the potential for harms.

Petrov et al reported on the safety profile of 495 venoplasty procedures performed in 461 patients with MS, including 98 stent implantations.¹⁷ There were no deaths, major bleeding events, or acute exacerbations of MS. The most common procedure-related complication was vein dissection, which occurred in 3.0% of cases. Other complications included cardiac arrhythmias (1.2%), groin hematoma (1.0%), vein rupture (0.4%), and acute stent thrombosis (1.6%).

Mandato et al reported on adverse events within 30 days of an endovascular intervention for 240 patients with MS over an 8-month period.¹⁸ Neck pain occurred in 15.6% of patients, most commonly following stent implantation. Headache occurred in 8.2% of patients and persisted

more than 30 days in 1 (0.4%) patient. Intraoperative arrhythmias occurred in 1.3%, and 1 patient was diagnosed with a stress-induced cardiomyopathy following the procedure.

Section Summary: Treatment of CCSVI With Percutaneous Venoplasty

A 2014 prospective, double-blind, sham-controlled RCT of venous angioplasty in MS patients with CCSVI showed no significant differences in venous outflow characteristics between the treatment and control groups, nor any significant improvements in clinical disease scores among treated patients and controls. The results of this RCT are limited by the small number of patients. A few case series of several hundred patients have reported on adverse events. They have established that adverse events are uncommon following venoplasty, but serious adverse events do occur. FDA issued an alert in 2012, noting the existence of serious reported complications, including death, and the need for ongoing monitoring. The published literature does not currently allow accurate estimates of rates of serious adverse events.

Summary of Evidence

For individuals who have multiple sclerosis (MS) who receive ultrasound with or without magnetic resonance imaging to diagnose chronic cerebrospinal venous insufficiency (CCSVI), the evidence includes systematic reviews and controlled observational studies. Relevant outcomes are test accuracy, test validity, and other test performance measures. Systematic reviews have generally found a statistically significant association between CCSVI and MS, but a 2014 meta-analysis that excluded studies by Zamboni (who proposed criteria for defining CCSVI) and associated research groups found no significant association. Moreover, systematic reviews have reported significant heterogeneity among studies. Recent observational studies have not found that Zamboni criteria or updated criteria proposed by the International Society for Neurovascular Disease can discriminate between patients with and without MS. The association between CCSVI and MS, especially as a causative factor, remains unclear. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have MS and CCSVI who receive treatment for CCSVI with percutaneous venoplasty, the evidence includes 1 randomized controlled trial (RCT) and several case series. Relevant outcomes are overall survival, symptoms, quality of life, and treatment-related morbidity. The RCT was double-blind and sham-controlled. It found no statistically significant differences in venous outflow characteristics or improvements in clinical disease scores between groups treated with venoplasty and a sham intervention. The results of this RCT are limited by the potential for underpowering, and we did not identify any other RCTs on the efficacy of percutaneous venoplasty. Data on adverse events are available from the Food and Drug Administration (FDA) as well as larger published case series (ie, with several hundred patients). The case series found that adverse events were uncommon following venoplasty, but serious adverse events have been reported to FDA. FDA issued an alert in May 2012, noting the existence of serious complications, including death, and the need for ongoing monitoring. It is not currently possible from the available literature to estimate with confidence the rate of serious adverse events (eg, death, major bleeding). The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

International Society for Neurovascular Disease

In 2014, the International Society for Neurovascular Disease published a position statement on detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency (CCSVI).² The document concluded:

"Although some CNS [central nervous system] disorders have been linked to the presence and severity of CCSVI, the ultimate cause-consequence relationship has not been firmly established. Therefore, it is not clear at this time which patient population should undergo the noninvasive and invasive studies for detection of extracranial venous abnormalities...."

Cardiovascular and Interventional Radiological Society of Europe

A 2011 Cardiovascular and Interventional Radiological Society of Europe (CIRSE) commentary on the treatment of CCSVI noted that:

"Thus far, no trial data are available, and there is currently no randomized controlled trial (RCT) in progress. Therefore, the basis for this new treatment rests on anecdotal evidence and successful testimonies by patients on the Internet. CIRSE believes that this is not a sound basis on which to offer a new treatment, which could have possible procedure-related complications, to an often desperate patient population."¹⁹

Society for Interventional Radiology

In 2010, the Society for Interventional Radiology (SIR) published a position statement on the association between CCSVI and multiple sclerosis (MS) and on the efficacy of endovascular treatments.²⁰ Its recommendations included the following statements:

"At present, SIR considers the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS."

SIR strongly supports the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies, and is actively working to promote and expedite the completion of the needed studies."

National Institute for Health and Clinical Excellence

In 2012, the U.K.'s National Institute for Health and Clinical Excellence (NICE) published guidance on the use of percutaneous venoplasty to treat CCSVI in patients with MS.²¹ This guidance contained the following statements on the diagnosis and treatment of CCSVI:

"Current evidence on the efficacy of percutaneous venoplasty for chronic cerebrospinal venous insufficiency (CCSVI) for multiple sclerosis (MS) is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research."

NICE encourages further research on percutaneous venoplasty for CCSVI for MS, in the form of robust controlled clinical trials. Studies should clearly define selection criteria and patient characteristics. They should also clearly define technical success which may include measurement of pressure gradients across treated vein segments before and after venoplasty. Outcomes should include clinical and quality of life measures."

European Society of Neurosonology and Cerebral Hemodynamics

The European Society of Neurosonology and Cerebral Hemodynamics (ESNCH) issued a statement on CCSVI and MS in 2012.²² The ESNCH statement indicated that the proposed criteria

for the diagnosis of CCSVI were questionable because of methodologic and technologic errors as well as lack of validation. The statement strongly discouraged any interventional treatment for CCSVI in MS, such as transluminal angioplasty and/or stenting, due to lack of evidence and risk of serious complications.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT01864941	Interventional Clinical Trial for CCSVI in Multiple Sclerosis Patients	100	May 2017

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 37238 Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; initial vein
- 37239 Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; each additional vein (List separately in addition to code for primary procedure)
- 37248 Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; initial vein
- 37249 Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; each additional vein (List separately in addition to code for primary procedure)
- 61630 Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous
- 61635 Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed

DIAGNOSES

Experimental / investigational for all diagnoses related to this medical policy.

REVISIONS

01-30-2012	Policy added to the bcbsks.com web site.
09-18-2012	Description section updated.
	Rationale section added.
	References section updated.
10-08-2013	Description section reviewed
	Rationale section updated
	References updated
11-24-2015	Description section updated
	Rationale section updated
	References updated
01-01-2017	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT Codes: 37246, 37247, 37248, 37249 (Effective January 1, 2017) ▪ Removed CPT Codes: 35460, 35476, 75978 (Effective December 31, 2016)
08-01-2016	Policy published 07-01-2017. Revision effective 08-01-2016. Thirty days notice given due to coding changes.
	Description section updated
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT Codes: 37238, 37239, 61630, 61635 ▪ Removed CPT Codes: 37246, 37247
	References updated

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