Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis
Second Report for CIHR Expert Panel
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Andreas Laupacis, MD, MSc[1,2]
Erin Lillie MSc[1]
Andrew Dueck, MD, MSc[2,3]
Richard Aviv, MBChB, FRCR[1,4]
Sharon Straus, MD, MSc[1,2]
Laure Perrier, Med, MLIS[1,5]
Jodie Burton, MD, MSc[6]
Kevin Thorpe, MMath[1,7]
Thomas Feasby, MD[8]
Julian Spears[1,2]

1. Keenan Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto
2. Faculty of Medicine, University of Toronto
3. Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto
4. Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto
5. Office of Continuing Education and Professional Development, Faculty of Medicine, University of Toronto
6. Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary
7. Dalla Lana School of Public Health, University of Toronto
8. Faculty of Medicine, University of Calgary

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Address correspondence to Dr. Andreas Laupacis. Li Ka Shing Knowledge Institute, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada
laupacisa@smh.ca

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List of abbreviations

CAL lesion: Calvarial lesion

CVF: Cerebral venous flow

CCSVI: Chronic cerebrospinal venous insufficiency

CE MRV: Contrast enhanced magnetic resonance venography

CI: Confidence interval

CIHR: Canadian Institutes of Health Research

CIS: Clinically isolated syndrome

CMAJ: Canadian Medical Association Journal

CSA: Cross-sectional area

CV: Contrast venography

dCVF: Change in cerebral venous flow

EDSS: Expanded Disability Status Scale

HC: Healthy controls

IJV: Internal jugular vein(s)

MRI: Magnetic resonance imaging

MRV: Magnetic resonance venography

MS: Multiple sclerosis

MSFC: Multiple Sclerosis Functional Composite scale

OND: Other neurological diseases

OR: Odds ratio

PC MRV: Phase contrast magnetic resonance venography

PP: Primary progressive multiple sclerosis

PTT: Partial thromboplastin time

RR: Relapse-remitting multiple sclerosis

SP: Secondary progressive multiple sclerosis

TAV: Time average velocity

TCD: Transcranial Doppler

TOF: Time-of-flight

TRICKS: Time Resolved Imaging of Contrast Kinetics

US: Ultrasound

VHISS: Venous Hemodynamic Insufficiency Severity Score

VV: Vertebral vein(s)

Executive Summary

Background

Zamboni has proposed that multiple sclerosis (MS) is caused by abnormalities in the anatomy and flow of the cerebral veins, which he has called chronic cerebrospinal venous insufficiency (CCSVI). This systematic review is an update of a systematic review initially presented to the Canadian Institutes of Health Research in June 2011, which reviewed the evidence regarding the association between venous abnormalities and MS, and the benefits and harms of endovascular treatment for CCSVI in patients with MS. The original review can be found at http://www.cihr-irsc.gc.ca/e/44356.html.

Methods

Studies assessing ultrasound and magnetic resonance venography (MRV) were given priority if they compared MS patients with patients without MS [either healthy controls (HC) or patients with other neurological diseases (OND)]. Only randomized trials were thought to provide good evidence about the benefits of endovascular treatment for MS; therefore these studies were given priority. To assess the harms of endovascular treatment, we gave priority to observational studies of >10 patients. An extensive literature search of peer-reviewed publications, with no language restrictions, was undertaken to identify eligible studies. Studies using ultrasound were statistically combined using a random effects model.

Results

Diagnosis of CCSVI with ultrasonography:

Nine studies compared the frequency of CCSVI diagnosed with ultrasound in MS patients with HC, and 5 studies compared MS patients with OND. CCSVI was diagnosed more frequently in patients with MS than in HC [odds ratio (OR) 12.8, 95% CI 2.8-59.1], but there was extensive heterogeneity. There continued to be a statistically significant association in the most conservative analysis, which involved removing Zamboni's initial study and adding a study in which no CCSVI was found in any patient (OR 4.0, 95% CI 1.4-11.0). The 5 studies that compared MS patients and OND patients found a higher frequency of CCSVI in MS patients, but this finding was not statistically significant (OR 32.5, 95% CI 0.6-1776.0); removal of Zamboni's study and adding a study in which no CCSVI was seen in any patient resulted in an OR of 2.4 (95% CI: 0.8-7.9). None of the studies using ultrasound reported the success of blinding of the technicians or radiologists.

A study of 710 MS patients in six centers found a large variation in the frequency with which the individual CCSVI criteria were positive, despite all centers being trained by Zamboni. This suggests the need for further standardization of the technique and/or interpretation of ultrasonography to diagnose CCSVI.

Magnetic Resonance Venography (MRV)

Only 3 small studies evaluated MRV findings in patients with MS and HC, and they found no statistically significant differences.

Contrast venography: One study of CV in 42 patients with MS found that 1/11 (9%) of patients with clinically isolated syndrome had extracranial venous stenosis, compared to 6/18 (33%) of patients with early relapsing remitting MS and 11/13 (85%) of patients with long-standing MS.

Endovascular treatment for CCSVI

One pseudo randomized trial of 15 patients comparing immediate with delayed endovascular treatment has been published – the poor study design and small number of patients means that the impact of this intervention upon the symptoms and signs of MS cannot be reliably assessed. Six studies reported peri-procedure complications of endovascular therapy in a total of 1148 patients. There were no deaths, and serious peri-procedure side-effects occurred in <2% of patients. The most frequent serious adverse effect was cardiac arrhythmia during the procedure, which occurred in between 1-2% of patients. Restenosis 6 to 18 months after endovascular therapy was reported in between 29% and 47% of patients. One study followed 240 patients for 30 days after endovascular therapy and found one patient with stent thrombosis one week later, but no other major complications. However, serious medium to long-term complications after endovascular therapy have been reported, such as stent migration, serious hemorrhage, pulmonary embolism, thrombosis of the internal jugular vein requiring thrombectomy, and death. More studies of long-term follow-up after endovascular therapy are needed.

Conclusion

A meta-analysis of 9 studies found a positive association between CCSVI and MS patients (compared to HC) that was statistically significant, even when a "conservative" analysis was conducted. However, poor reporting of the success of blinding, and the marked heterogeneity of the results do not allow definitive conclusions to be reached. Further high quality studies, using standardized ultrasound techniques and careful measurement of the reproducibility of the technique, are needed to definitively determine whether CCSVI is more frequent in patients with MS than those without MS. Endovascular therapy is associated with serious peri-procedure adverse events in <2% of patients. However, because of the poor methodological quality of published studies evaluating the benefits of endovascular therapy for CCSVI in MS patients, the impact of treatment on radiological and patient-relevant outcomes is not known.

INTRODUCTION AND BACKGROUND

a) Venous abnormalities and MS

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system. The exact cause remains unknown, but evidence over the better part of a century has demonstrated that it is immune-mediated and likely an autoimmune disease. MS can take two main forms clinically - relapsing and/or progressive. Roughly 85% of patients present with relapsing-remitting disease while the remainder present with primary progressive MS. A proportion of relapsing patients will convert to progressive disease over time. While moderately effective disease-modifying drugs to prevent relapses have been available for many years, there is no cure for MS, and no therapy proven to prevent progression.

In 2006, Dr. Paulo Zamboni and colleagues proposed a new etiology for MS (1). They have subsequently reported that patients with MS have a higher frequency of abnormalities of anatomy and flow in the internal jugular, deep cerebral, vertebral and azygous veins than individuals without MS (2-10). They have called this entity chronic cerebrospinal venous insufficiency (CCSVI), and postulated that CCSVI causes abnormal iron deposition in the brain, which triggers an autoimmune reaction leading to the development of MS.

CCSVI as described by Zamboni et al is detected by transcranial and extracranial Doppler ultrasound. It requires the evaluation of 5 ultrasound parameters - see the Results section for a description of the parameters. CCSVI is diagnosed if a patient has an abnormality in 2 or more of the 5 parameters. Ultrasonography has the advantage of being a non-invasive test with no known risks; however, it can be very operator-dependent.

Investigators, including Zamboni, have used other techniques to study cerebral venous flow and anatomy including magnetic resonance venography and direct venography.

- Magnetic resonance venography (MRV) can be used to image cerebral venous flow and anatomy. It is not as operator dependent as ultrasonography and does not expose the patient to radiation, although there are small risks associated with injection of contrast. It cannot be conducted if patients have severe claustrophobia, or have implanted electronic devices, non-MR-compatible cerebral aneurysm clips, and ferromagnetic foreign bodies in critical locations.
- Direct venography is still considered the ‘gold standard’ for visualization of cerebral venous anatomy. It involves inserting a catheter in the femoral vein and passing it through the right side of the heart into the proximal jugular, vertebral and azygos veins. It is by far the most invasive technique for visualizing the cerebral veins and is associated with exposure to contrast dye and ionizing radiation, cardiac arrhythmias and hematomas and (rarely) aneurysms in the groin.

A number of studies have been published using the diagnostic tests described above that have evaluated the frequency of cerebral venous abnormalities in patients with MS compared with individuals without MS. An important focus of this report is to describe and systematically review the peer-reviewed literature assessing the potential association between venous abnormalities and MS.

b**) Treatment of CCSVI**

In 2009, Dr. Zamboni and colleagues published the results of an un-blinded, non-controlled observational study of venoplasty in 65 consecutive MS patients with CCSVI (11). They reported a "minor and negligible" peri-procedure complication rate, a lowering of post-intervention venous pressure and an improvement in relapse rate and functional scores in the sub-group of patients with relapsing-remitting MS. After 18-months of follow-up, re-stenosis occurred in 47% of patients.

Despite the poor methodological quality of Zamboni's study (he called for randomized trials to further assess the benefits and harms of endovascular therapy for CCSVI), numerous clinics outside of Canada are offering this procedure, and many MS patients are undergoing it. Three randomized trials of endovascular therapy for MS have been registered with clinicaltrials.gov (http://clinicaltrials.gov/ct2/results?term=ccsvi) but none have yet been reported.

Because of the variable course of MS and the subjective nature of many of its symptoms, we believe that only double-blind randomized trials can provide convincing information about the impact of endovascular therapy on the symptoms and signs of MS. No randomized trials have yet been published. One small pseudo-randomized trial (12) and four observational studies with no control groups have been published (11,13-15). Though the lack of a control group in the four observational studies and the small size of the quasi-randomized trial make their results hard to interpret, we summarize their findings in section D of the Results section of this report.

Well reported observational studies provide useful information about the harms of endovascular therapy such as arrhythmias, stent migration, re-stenosis and death. This report describes and systematically reviews the peer-reviewed literature about the harms of endovascular therapy for MS.

METHODS

a) Literature searches

Only articles in peer-reviewed publications were accepted. In order to identify eligible publications, two literature searches of the following electronic databases were conducted: Ovid MEDLINE (2005 to September, 2011), the Cochrane Central Register of Controlled Trials (2005 to September, 2011) and EMBASE (2005 to September, 2011). No language restrictions were imposed.

For the studies of association between cerebral venous abnormalities and multiple sclerosis, the following search terms were used: multiple sclerosis, ultrasonography, Doppler, phlebography, angiography, and venography. For the studies of the benefits and harms of venoplasty or stenting of cerebral veins in MS patients, the following search terms were used: multiple sclerosis, stents, chronic cerebrospinal venous insufficiency, and venoplasty. In both cases, appropriate wildcards were used in the searching in order to account for plurals and variations in spelling. The detailed search strategies are shown in the Appendix.

Reference lists of all articles meeting eligibility criteria, in addition to review articles, were examined to identify publications that may have been missed by our literature searches. We also asked members of the CIHR scientific expert working group to identify any relevant studies.

b) Identification of articles for inclusion

The focus of our systematic review of studies of association was on studies that met all of the following criteria: reporting of original data in a peer-reviewed publication; use of either Doppler ultrasonography or magnetic resonance venography; and assessment of patients with MS and at least one control group (the control group could be healthy controls or patients with neurological disorders other than MS). Because subjecting control group patients without MS to direct venography is unethical, we accepted studies of contrast venography without a control group. For completeness, we also briefly describe diagnostic studies relevant to CCSVI and MS that did not meet these methodological criteria and were published since June 2011.

We also sought any studies that reported the reliability of the various tests.

Regarding the benefits and harms of endovascular therapy, we focused on randomized trials, but also describe observational studies that reported on the benefits or harms of endovascular therapy. Case reports of harms of endovascular therapy were also sought.

The titles and abstracts of all studies identified were screened independently by two reviewers (Andreas Laupacis, Sharon Straus) to select articles that might meet the eligibility criteria. Any study that might have relevant information was selected.

The full texts of all articles considered to be potentially eligible were assessed independently by two reviewers (Andreas Laupacis, Sharon Straus) with the aim of identifying studies meeting the inclusion criteria. Disagreements were resolved by consensus, or involvement of a third reviewer (Andrew Dueck). Articles that were considered eligible after the full-text review were the final set of studies included in the review.

c) Abstraction of data

Each included article was given a unique ID number and after pilot-testing a data abstraction form, two reviewers independently extracted data and carried out a methodological quality assessment (using items derived from the Newcastle-Ottawa

Quality Assessment Scale tool for observational studies for the studies of association (16). Disagreements were resolved by consensus.

d) Presentation of data

Ten studies that described the association between CCSVI diagnosed by ultrasonography and MS were considered similar enough to allow statistical meta-analysis (3,17-25). The Cochrane Review manager 5.1, Version 5.1.2 was used to generate odds ratios and Forest plots, determine whether there was a statistical association between CCSVI and MS (using a random effects model), and assess for heterogeneity. Heterogeneity was quantified using the I^2 statistic.

RESULTS

I: Identification of eligible studies

Figures 1 and 2 display the results of the literature searches and evaluation of potentially eligible articles.

Figure 1a: Identification of Studies of Association: Results of Initial Literature Search (2005 – June 28, 2011)

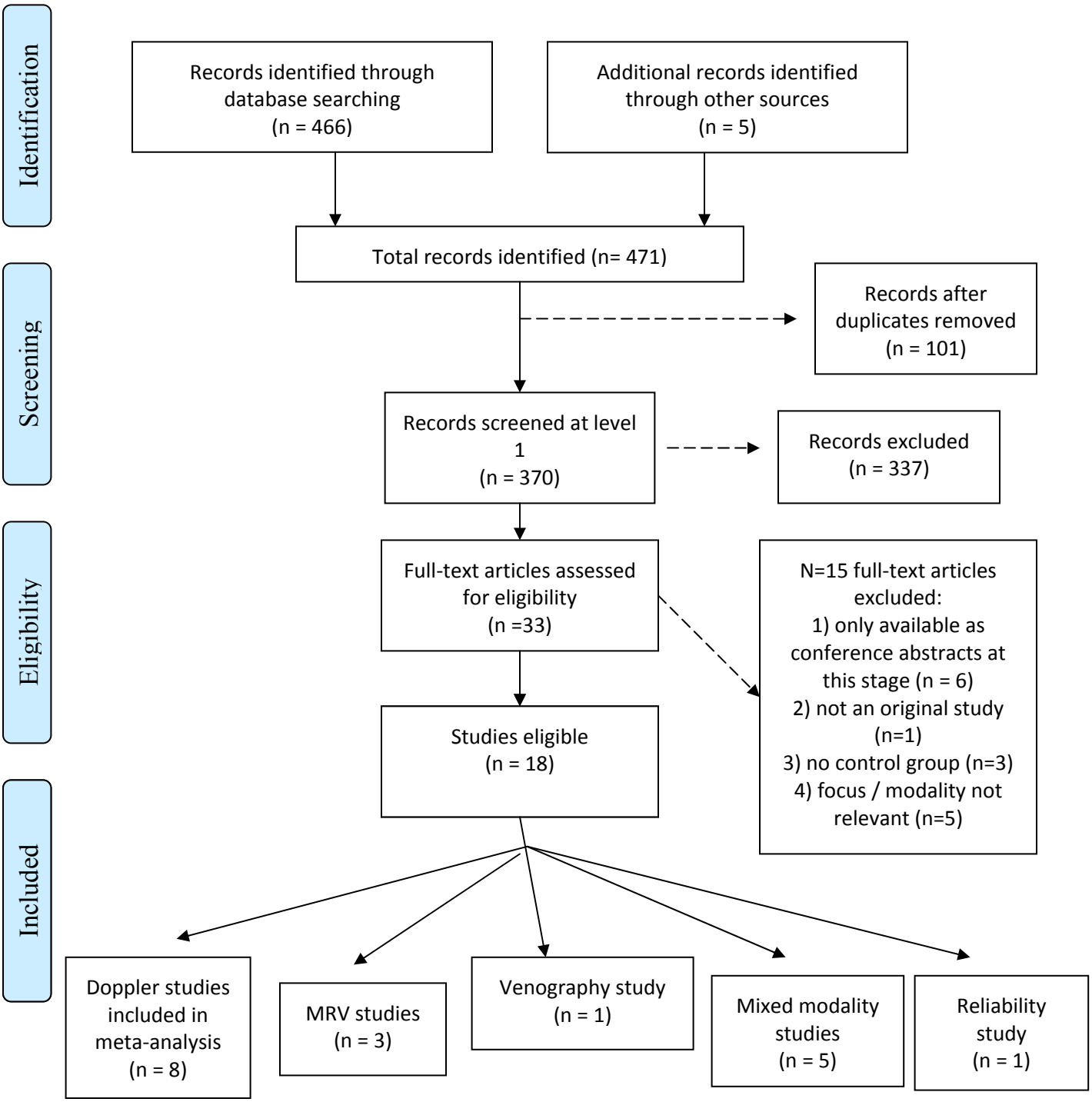


Figure 1b: Identification of Studies of Association and Other Diagnostic Studies: Results of Literature Search Update (2005 – September, 2011)

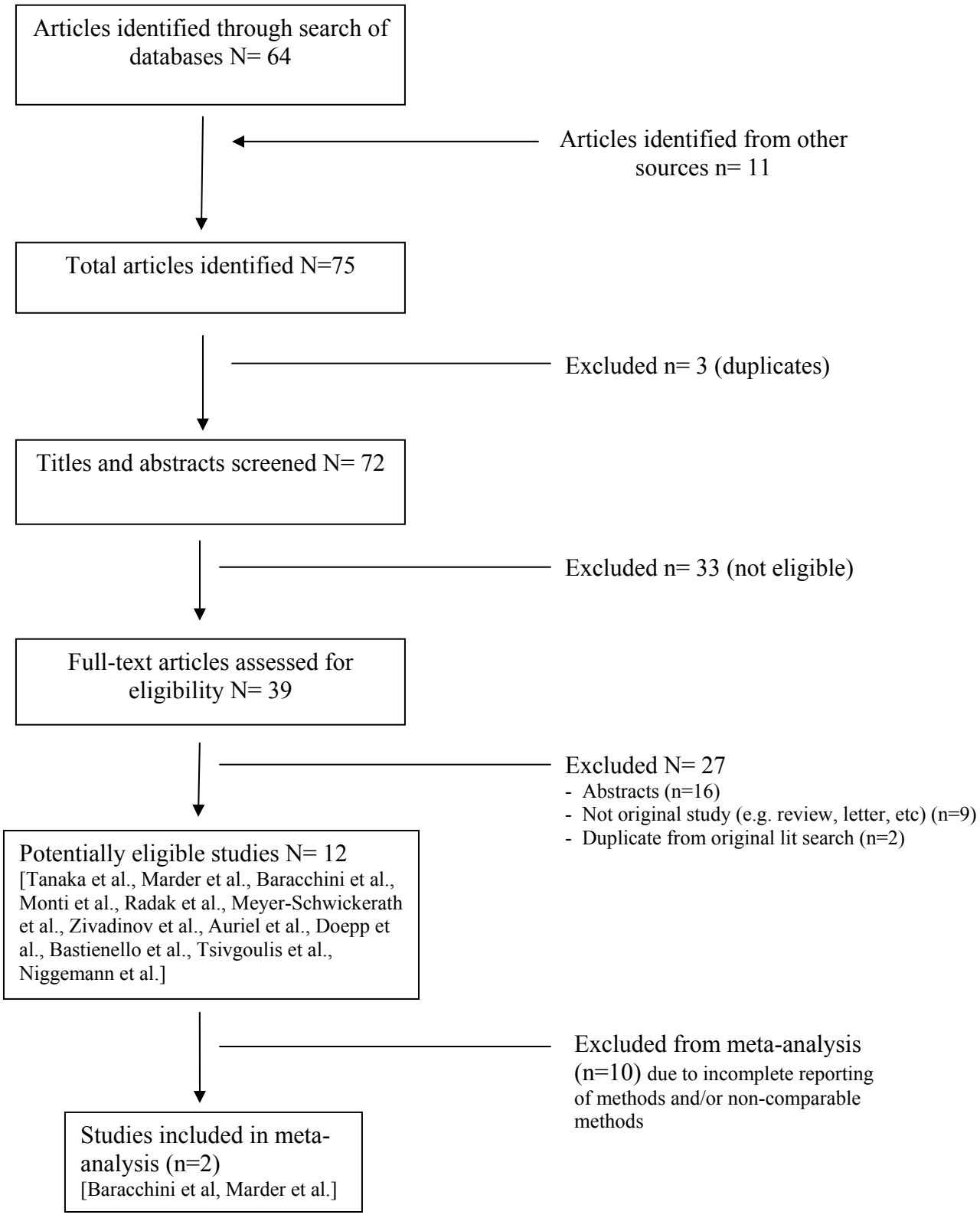


Figure 2a: Identification of Studies of Adverse Effects of Endovascular Interventions for CCSVI: Results of Initial Literature Search (2005 – June 28, 2011)

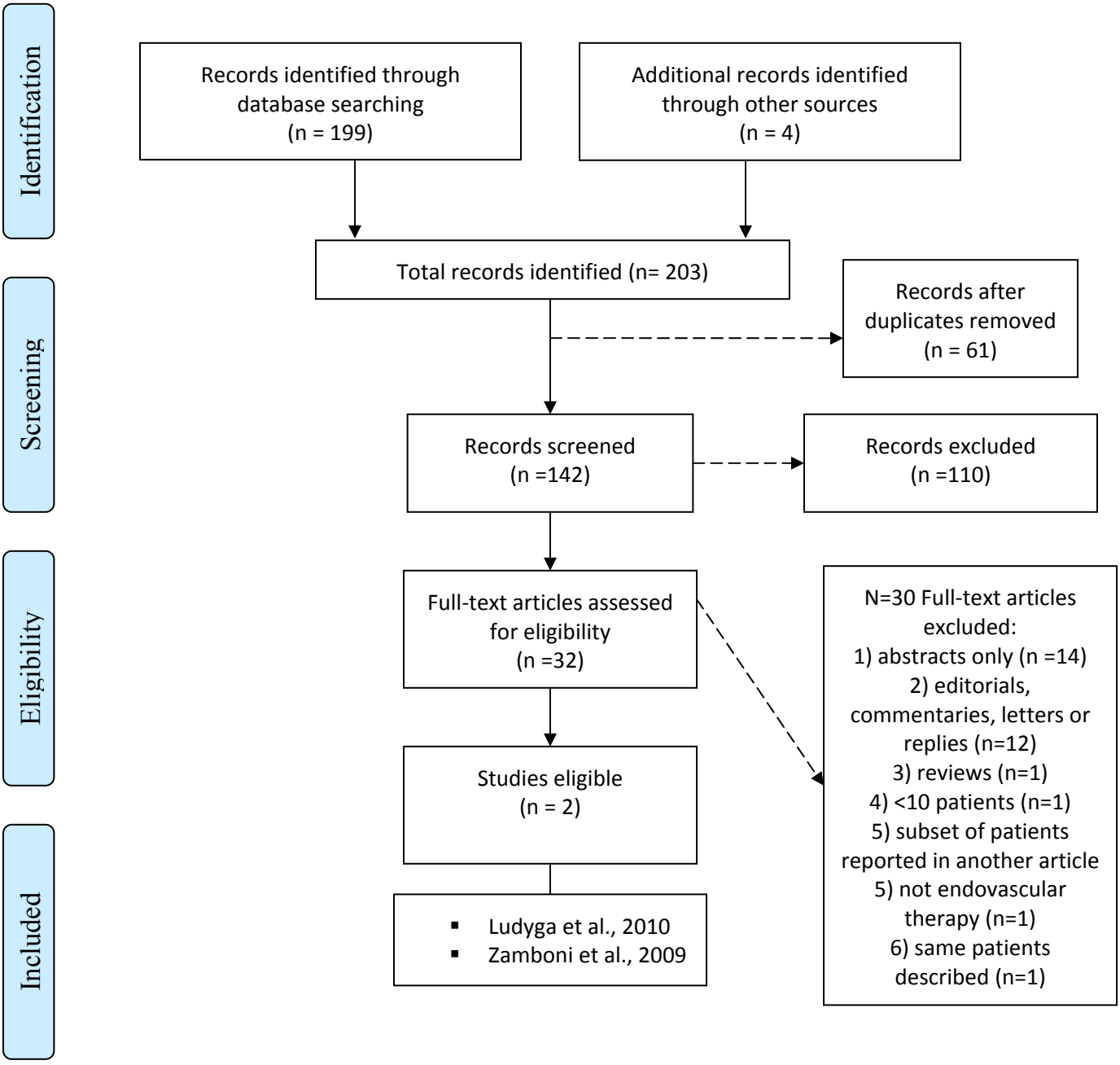
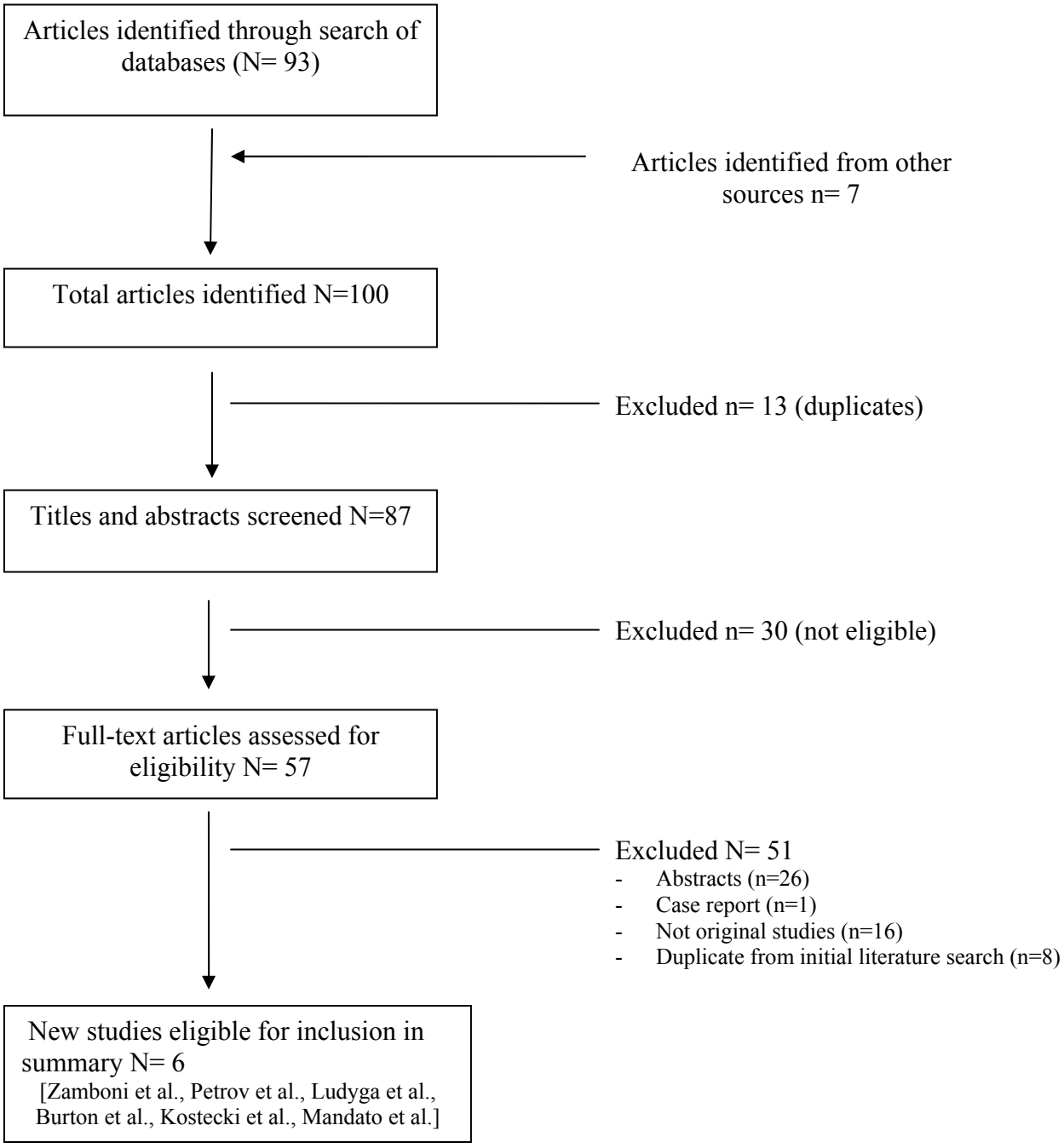


Figure 2b: Identification of Studies of Benefits and Harms of Endovascular Interventions for CCSVI: Results of Literature Search Update (2005 – September, 2011)



II. Descriptions and results of studies of association

A) Studies of association between MS and CCSVI measured using ultrasound

a) Meta-analysis of studies using ultrasonography to diagnose CCSVI

At the time of the first report to the CIHR, we found eight studies that examined the association between CCSVI diagnosed by Doppler ultrasonography and MS. These studies each had a control group of healthy controls, patients with other neurological diseases or both. The results of these studies were combined in a meta-analysis and published in the Canadian Medical Association Journal in October 2011– see *Systematic review of the association between chronic cerebrospinal venous insufficiency and multiple sclerosis*, available at: www.cmaj.ca/lookup/doi/10.1503/cmaj.111074.

The main findings of the CMAJ publication were summarized in the abstract:
Background: *It has been proposed by Zamboni and colleagues that multiple sclerosis is caused by chronic cerebrospinal venous insufficiency, a term used to describe ultrasound-detectable abnormalities in the anatomy and flow of intra- and extracerebral veins. We conducted a meta-analysis of studies that reported the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis.* ***Methods:*** *We searched MEDLINE and EMBASE as well as bibliographies of relevant articles for eligible studies. We included studies if they used ultrasound to diagnose chronic cerebrospinal venous insufficiency and compared the frequency of the venous abnormalities among patients with and those without multiple sclerosis.* ***Results:*** *We identified eight eligible studies: all included healthy controls, and four of them also included a control group of patients with neurologic diseases other than multiple sclerosis. Chronic cerebrospinal venous insufficiency was more frequent among patients with multiple sclerosis than among the healthy controls (odds ratio [OR] 13.5, 95% confidence interval [CI] 2.6–71.4), but there was extensive unexplained heterogeneity among the studies. The association remained significant in the most conservative sensitivity analysis (OR 3.7, 95% CI 1.2–11.0), in which we removed the initial study by Zamboni and colleagues and added a study that did not find chronic cerebrospinal venous insufficiency in any patient. Although chronic cerebrospinal venous insufficiency was also more frequent among patients with multiple sclerosis than among controls with other neurologic diseases (OR 32.5, 95% CI 0.6–1775.7), the association was not statistically significant, the 95% CI was wide, and the OR was less extreme after removal of the study by Zamboni and colleagues (OR 3.5, 95% 0.8–15.8).* ***Interpretation:*** *Our findings showed a positive association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions.*

Since our first report (26), two recently published studies were found to meet our eligibility criteria (24,25) and have been added to the meta-analysis. A third study (27) described the frequency of three of the five CCSVI criteria in 42 MS patients and 43 healthy controls, but did not report the frequency of CCSVI. This study is briefly described at the bottom of page 13. Two other studies reported ultrasound findings in

patients with MS and a non-MS control group but were so poorly reported that data could not be abstracted and they were excluded from this analysis (28,29).

Tables 1-4 describe the characteristics of all ten studies included in the meta-analysis, and the patients enrolled in them. The results of the updated meta-analysis are shown in Figures 3-9. Because the two new studies were very small (see below), the results of the meta-analysis are essentially unchanged from the paper published in the Canadian Medical Association Journal. The odds ratio comparing the frequency of CCSVI in MS patients with healthy controls is 12.8 (95% CI 2.8-59.1). The most "conservative" sensitivity analysis (removing Zamboni's study and adding Doepp's study which did not find CCSVI in any patients) yields an OR of 4.0 (95% CI 1.4-11.0). The odds ratio comparing the frequency of CCSVI in patients with MS and patients with other neurological disorders is unchanged (OR 3.5; 95% CI 0.8-15.8). When Marder's study, which did not find CCSVI in any patient, is added, the OR is 2.4 (95% CI: 0.8-7.9).

A brief description of each of the ten studies in the updated meta-analysis is provided below.

The Zamboni study (3) that was included in this meta-analysis was the study from his group that reported the largest number of patients – 109 patients with MS and 177 controls. The controls consisted of young healthy controls, older healthy controls and individuals with other neurological diseases. However, the MS patients were not compared with each of the control groups separately – the controls were combined together when compared with the MS patients. Zamboni's findings are exceptional because he found that all patients with MS had CCSVI compared with none of the controls. Zamboni reported that his study was blinded, but did not describe the mechanism of blinding nor did he test for the success of blinding.

Zivadinov's study (23) appeared to be the highest quality of the 8 studies included in this meta-analysis. Its sample size was the largest (289 patients with MS, 210 controls), the investigators described their ultrasound technique in great detail, and they provided a detailed description of their mechanism of blinding (although they did not test the success of blinding at the end of each examination). Zivadinov's study was the only one other than Al-Omari (17) to describe difficulty assessing some of the Doppler criteria – specifically parameter 2 (reflux in the deep veins). He was unable to assess deep vein reflux in 125 of 499 (28%) subjects.

Baracchini (18) studied patients with clinically isolated syndrome, and as would be expected, their mean EDSS scores were low. He studied three different controls – young individuals who were age and gender matched to the patients with clinically isolated syndrome, a group of patients with other neurological diseases, and healthy controls age and gender matched to the OND patients. He found a low prevalence of CCSVI in patients with CIS (8/50- 16%), no CCSVI in the 60 (0%) patients with OND and 1 individual with CCSVI in 110 (1%) healthy controls. Because of the very low frequency of CCSVI in non-MS individuals, there was a statistically significant OR when comparing the frequency of CCSVI in MS patients compared to healthy controls and

OND patients. He indicated that the study was blinded, but did not describe how, nor did he describe testing the success of blinding.

Centonze's technician was trained by Zamboni, and used the same type of ultrasound machine as Zamboni. Centonze (19) reported considerable difficulty evaluating criterion 2 (reflux in the deep veins). He did not report data on the individual criteria separately, but only reported whether or not patients had CCSVI. He found CCSVI in 42/84 (50%) of the MS patients, which was non-statistically significantly higher than in healthy controls (20/56; 36%). He indicated that the analysis was blinded but did not describe how blinding was attempted, or report data on whether blinding was successful.

Al-Omari's study was unblinded (17). He did not attempt to assess parameter 2, yet despite that, reported that 21/25 (84%) patients with MS had CCSVI compared with none of the 25 healthy controls. He reported parameter 3 in a manner that made it impossible to determine how many patients were positive for parameter 3.

Mayer (22) described a sophisticated method of blinding, but did not describe the success of blinding. He appeared to use a slight modification of the Zamboni criteria, especially parameter 5. He found no CCSVI in 20 (0%) MS patients and 1 in 20 (5%) healthy control patients.

Doepp's study (20) did not describe an attempt at blinding – therefore, it was presumably not blinded. He found no cases of CCSVI among 56 patients with MS and 20 healthy controls.

Krogias (21) reported an unblinded study of 10 patients with MS and 5 patients with OND and 2 healthy controls; 2 (20%) MS patients and 0 (0%) controls had CCSVI.

Marder and colleagues (25) conducted a study of 18 patients with MS and 11 controls. Some of the controls had migraines while the others were described as "individuals without a neurological diagnosis". For the purposes of the meta-analysis, we categorized the controls as patients with other neurological diseases. Marder et al indicated that their study was blinded, but provided no details about how blinding was achieved or how successful it was. They found no CCSVI in any of the study subjects (they do not report the number of controls with CCSVI in their paper, but they confirmed in a personal communication that no controls had CCSVI).

Baracchini and colleagues (24) conducted a study in 60 patients with progressive MS and 60 age and sex matched healthy controls. Blinding was quite well described, but the success of blinding was not described. They found CCSVI in 4/60 patients with MS (7%) and in none of the healthy controls.

Tsivgoulis and colleagues (27) studied 42 patients with MS and 43 healthy controls to determine the frequency of CCSVI in the two groups. The study was blinded - patients were placed in the examination chair before the ultrasonographers entered the room, and the ultrasonographers avoided all conversations with the study subjects. Thus, they

appeared to make an excellent attempt at blinding, although the success of blinding was not documented. The ultrasonographers were not trained by Zamboni. They found fair or poor intra and inter-observer agreement for two CCSVI criteria – reflux in the deep cerebral veins and the difference in the cross sectional area of the internal jugular vein between the supine and upright position (kappa values ranging from 0.14-0.48). Because of the poor reproducibility, they did not record the frequency of abnormalities for these criteria, and therefore could not assess the frequency of CCSVI. The agreement for the other three CCSVI criteria was good (kappa 0.82-1.00). The investigators found reflux in the internal jugular and vertebral veins in only 2% of MS patients and controls, and did not find jugular vein stenosis or absence of Doppler flow in the jugular or vertebral veins in any patients.

b) Reproducibility of CCSVI assessment

One paper's title indicated that it had studied the inter-rater reliability of CCSVI assessment (5). However, neither of our 2 independent reviewers could find data in the paper describing inter or intra-rater reliability.

Zivadinov and colleagues (23) assessed intra-rater reliability of the diagnosis of CCSVI in 28 patients (11 with MS) one week apart, and found an agreement of 89% and a kappa of 0.75. The classification changed in 3/28 (11%) patients – one borderline diagnosis was changed to abnormal, and 2 normal diagnoses were changed to abnormal.

Tsivgoulis and colleagues (27) found fair or poor intra and inter-observer agreement for two CCSVI criteria – reflux in the deep cerebral veins and the difference in the cross sectional area of the internal jugular vein between the supine and upright position (kappa values ranging from 0.14-0.48). The agreement for the other three CCSVI criteria was good (kappa 0.82-1.00).

B) Studies of the frequency of venous abnormalities in MS patients compared to healthy controls using Magnetic Resonance Venography (MRV)

a) Eligible studies

Three studies reported information about MRV findings in unselected patients with MS and healthy controls (30-32), and met our eligibility criteria for inclusion in this systematic review. A second study by Zivadinov (33) reported on 10 MS patients and 6 healthy controls. However, this study was not eligible because the MS patients were all participants in Zamboni's study of endovascular treatment (11) , had been diagnosed with CCSVI, and all had venographic evidence of anatomical abnormalities in at least one IJV; they were therefore highly selected MS patients. We also excluded a study of 10 MS patients and 7 controls by Hojnacki (4) because all MS patients had CCSVI diagnosed by ultrasonography, and the study appeared to include the same patients as Zivadinov's study (33).

The characteristics of the three eligible studies (30-32) and the patients enrolled in them are shown in Tables 4 and 5. The studies were conducted in the United States, Sweden and the Netherlands. The studies were small, with a total of 98 patients with MS (range

20 to 57) and a total of 60 age and gender-matched healthy controls (20 controls in each study).

Zivadinov (32) prospectively studied 57 consecutive MS patients and 21 controls. MRV images were interpreted independently by 2 radiologists with 3 and 5 years experience. IJV morphological features were evaluated using a 2D TOF and 3D TRICKS sequence to assess structural lumen characteristics.

TOF MRI is a contrast independent technique that uses gradient echo sequences to saturate the signal within stationary tissue accentuating signal from fully magnetized spins contained within new blood entering a region of interest. 2D TOF is more sensitive to slow flow by virtue of multiple contiguous axial slices but is usually associated with lower z-plane resolution than 3D TOF techniques. TRICKS is a contrast dependent technique that sacrifices spatial for temporal resolution, allowing temporal acquisition of angiographic images which may be viewed as a cine or reconstructed into more conventional static angiographic images.

Only 7 of the 21 control patients in Zivadinov's study underwent TRICKS evaluation because the others declined to have an injection of contrast agent. The investigators used a qualitative score to assess the IJV morphology as absent, pinpoint, flattened, crescentic and ellipsoid. Measurements were made within the upper and lower segment of the vessel divided by an imaginary line drawn midway between the jugular bulb and the innominate vein, considering the narrowest part in each of 4 vessel segments. They considered absent and pinpoint to be abnormal. With TOF, they found abnormalities in 31/57 (54%) MS patients and 9/21 (43%) healthy controls; with TRICKS they found abnormalities in 29/54 (54%) MS patients and 1/7 (14%) healthy control patients. These results were not statistically significant. They also assessed vertebral vein flow as present or absent, side-to-side IJV asymmetry as present or absent, and the presence of collateral veins. They found no difference between MS patients and controls in any of these three parameters.

Wattjes used contrast enhanced (CE MRV) and 2D phase contrast PC MRV to study 20 patients with MS and 20 controls (31). CE MRV was read in consensus by two interventional neuroradiologists while the PC was read independently by a physicist. All readers were blinded to the patients' diagnosis and to the other MR venographic sequence. They classified patients' venous flow as normal, possibly anomalous (stenosis with no collaterals), and probably anomalous (stenosis with collaterals). Anomalous findings were present in 10/20 (50%) MS patients and in 8/20 (40%) of healthy control patients. PC MRV was limited to the intracranial veins demonstrating no flow reversal in any patient. 2 MS and 2 HC each demonstrated almost zero flow in the straight sinus or left internal cerebral vein respectively. No comparison between the two MR techniques was intended or presented.

Sundstrom studied 21 patients with MS and 20 healthy controls using CE MRV of the head and neck and 2D PC MRV of the neck (30) . The PC data were read independent of the CE MRV. They assessed total cerebral blood flow by summing the average flow rate in the carotid and vertebral arteries. Total IJV flow was determined by summing the

average flow rate of each IJV. To control for differences in IJV blood flow between cases and controls, the total IJV flow was expressed as a proportion of the total cerebral blood flow. There was no statistically significant difference between MS patients and healthy control patients in total cerebral blood flow (723+/-123 mL/min in MS vs 813+/-184 mL/min in HC; p=0.07), or normalized IJV flow (70%+/-21 in MS vs 70%+/-13; p=0.38). Three of the 21 MS patients had a stenosis in the mid portion of an IJV; the other 18 patients had no evidence of stenosis. Reflux was present in 5/21 MS and 5/20 control patients.

Zivadinov and others used 2D TOF and TRICKS sequences in their MRV studies. 2D TOF is a relatively simple MRV technique that was developed for imaging vessel lumen signal. The technique suffers from relatively low spatial resolution and can easily be affected by flow artifacts which will alter the appearance of the lumen signal. It is important to recognize that although signal is generated by flow, the studies using this technique were measuring the shape of the signal created to infer structural morphology. This approach may be acceptable where vessels run perpendicular to the acquired slice (which is likely true for IJVs) but may be inaccurate where vessels are more tortuous or redundant. The vertebral venous plexus is a highly complex group of veins frequently showing redundancy and tortuosity. TOF techniques may not consistently depict true luminal structure for these vessels. None of the studies using TOF addressed these potential limitations. 3D TRICKS is an excellent technique for assessing temporal contrast passage. Its main application is in the context of vascular malformation imaging. It also provides information relating to direction of flow. In order to achieve the necessary temporal resolution however, both spatial and contrast resolution are forfeited. It is unclear why Zivadinov and the others who chose to use these two techniques did so. Several studies have compared spatial and contrast resolution of contrast enhanced sequences to TOF based sequences and almost invariably report superiority with contrast techniques. Only under the most sophisticated conditions (often confined to research rather than clinical environments) can a TOF sequence approach that of contrast techniques. This is also only true of the 3D TOF rather than 2D TOF techniques. Use of TOF techniques does provide the opportunity for controlling which direction of flow is being assessed by eliminating flow in the opposite direction by saturation pulse application. However, none of the studies utilizing TOF attempted to assess flow direction with this technique, further calling into question the reasoning for their selection. Overall it is our opinion that CE MRV techniques offer the best opportunity for high spatial resolution study of the veins. Limitations include inability to assess the effect of posture and respiratory phase on the appearance. Lastly it does not provide flow information.

b) Reproducibility of MRV findings

Zivadinov studied 6 MS patients and 6 healthy controls one week apart using 2D TOF and 3D TRICKS to assess image-reimage reproducibility (32). The kappa for TOF was 0.66 and for TRICKS was 0.33. The agreement between TOF and TRICK for IJV lumen morphology was modest (the kappa values were 0.26 absent, 0.56 pinpoint, 0.25 flattened, 0.20 crescentic and 0.59 ellipsoid). No significant image-reimage differences were found for vertebral veins, left-right asymmetries, or prominent collateral pathways.

c) Correlation between ultrasound and MRI findings

Doepp and colleagues (34) reported a single center prospective cross sectional study of 40 pts with MS, in which they correlated ultrasound findings with MRI findings. The hypothesis was that ultrasound should be able to detect MRV defined stenoses or the hemodynamic changes associated with these stenoses. The methodology was well described although the mechanism of patient recruitment was vague. The authors measured derived blood flow parameters by calculating blood volume flow and cross sectional area of both internal carotid arteries, vertebral arteries, vertebral veins and internal jugular veins. The azygos veins were also assessed for stenoses. Patients were assessed supine and upright by 2 blinded sonographers although the method of blinding from disability was not stated. Similarly 2 neuroradiologists assessed the MRI, independent of ultrasound results. Patients were divided into 3 categories of incremental stenosis based on MRV assessment at strict anatomical locations. The prevalence of MS subtype, disease duration, age and flow parameters, and change of parameters with posture were compared.

Although 48% of patients had between 50-80% stenosis on MRV, with another 22% having >80% stenosis, only 1 patient had stenosis on ultrasound. Four patients fulfilled 1 CCSVI criteria while none fulfilled 2 criteria. Based on these results, the authors argue that US is unreliable at detecting stenosis, and the much lower incidence of stenosis demonstrated relative to MRV would argue against the high values reported by other groups.

Another study of 10 MS patients with CCSVI and 7 healthy controls found high agreement between ultrasonography and MRV if the ultrasound showed no abnormality in the IJV, but low agreement if the ultrasound detected an IJV abnormality (33). This study needs to be replicated in other centers with larger sample sizes.

d) Other MRV studies that did not meet our inclusion criteria

Three studies that used MRV in MS patients did not meet the inclusion criteria for our meta-analysis either because they assessed highly selected MS patients or did not have a non-MS control group.

Hojnacki and Zivadinov reported on 10 MS patients who appear to be the same patients (4,33). Hojnacki reported on 7 controls, while Zivadinov reported on 6, so we describe Hojnacki's study. He reported on MRV findings in 10 MS patients who had CCSVI according to ultrasound criteria, and therefore were a highly selected group of MS patients. Three patients had abnormal TOF and 4 had abnormal TRICKS results on MRV. Of the 21 abnormalities detected in the IJVs by ultrasonography in both MS patients and controls, 4 were abnormal when assessed by TOF and 5 were abnormal when assessed by TRICKS. Of the 13 IJVs that were normal on ultrasound, 12 were normal when assessed by TOF and TRICKS.

Hartel from Poland used MRV to assess 830 patients with MS who had been diagnosed with CCSVI using ultrasonography (35). They provided a very limited description of the patient characteristics, and the methodology utilized to interpret their 2D TOF imaging

did not allow meaningful comparison with any other study. Therefore, data were not abstracted from this study.

C) Studies of contrast venography

Because of the invasive nature of contrast venography (CV) and its associated radiation exposure, CV is not an attractive screening test for venous abnormalities in patients with MS, and it would not be ethical to ask patients without MS to undergo CV. Therefore, no studies were found assessing the frequency of CV abnormalities in unselected patients with MS and controls.

a) Venography findings in MS patients

Only one study, from an MS clinic in Lebanon, has reported on CV findings in a convenience sample of MS patients (36). The mean age of the 42 patients studied was 37 years, 64% were female and the mean EDSS score was 1.5. Eleven patients had clinically isolated syndrome, 18 early relapsing-remitting MS and 13 late MS (mean duration of disease 14 years). The mean duration of disease for the clinically isolated syndrome and early relapsing remitting MS patients together was 2.3 years. CV was performed by a radiologist with 25 years of experience. This paper provided a high quality description of the venographic technique used. In addition to 50% stenosis definition, Yamout also assessed delayed clearance of contrast and the presence of valve leaflets. No manometry was performed. IJV stenosis was defined as 50% or greater narrowing of the lumen, delayed clearing of the contrast column across the lesion and absence of valve leaflets. Abnormalities in the azygos veins were "reported as observed". Extracranial venous stenoses were seen in 1/11 (9%) of patients with clinically isolated syndrome, 6/18 (33%) of early relapsing remitting MS and 11/13 (85%) of late relapsing remitting MS. Only 3 patients had two stenoses.

b) Venography in MS patients with CCSVI diagnosed with ultrasonography

We identified seven studies that reported CV results in patients who were found to have CCSVI on ultrasonography. The results of the studies varied considerably.

Two pairs of studies appeared to report on the same groups of patients: Bartolomei and Zamboni reported on the same 65 patients (2,8) (we have excluded Bartolomei's study), and Zivadinov and Hojnacki appear to report on the same 10 MS patients (4,33) (we have excluded Zivadinov's study). Thus, below we summarize the results of five studies that reported CV results in MS patients with CCSVI.

Zamboni reported that all 65 MS patients (100%) with CCSVI had significant extracranial venous stenoses (2). Venography was performed unblinded to patient diagnosis. No technical details were provided for the technique used, but stenosis was reported as a 50% lumen reduction and manometry was performed across any visualized stenosis. No information is provided about whether stenosis was assessed in both inspiratory and expiratory phases. Zamboni reported abnormal azygous veins in 86% of patients (most often membranous obstruction of the junction with the superior vena cava, twisting, or less often septum and atresia). The IJVs were stenosed unilaterally or bilaterally in 59/65 (91%) patients, most frequently annulus and septum.

Hojnacki reported finding at least one abnormality in all 10 (100%) of the MS patients with CCSVI whom he studied (4). There was a similar lack of technical information about the venographic technique as in Zamboni's paper (2). Again a 50% lumen reduction was considered abnormal. No manometry was provided. It is not clear whether these ten patients were included within the 65 reported by Zamboni.

Baracchini performed CV in 7 of 8 MS patients with CCSVI (18). The CV was normal in 6 of the 7 (14%) patients; the seventh patient had hypoplasia of the right IJV. Technical aspects of the venographic procedure were reasonably well reported. The authors performed venography with breath hold and also used 50% stenosis to define abnormal. More extensive investigation of each IJV stenosis was performed, including imaging any abnormality in both Valsalva and expiration. Manometry was also performed in supine and 45 degree positions for both IJVs.

In a second study by Baracchini and colleagues (24), they conducted a venogram in 3 of 4 patients with MS who they identified as having CCSVI. One of the three patients (33%) had an abnormal venogram (bilateral narrowing of the internal jugular veins).

Petrov and colleagues (37) reported on 461 patients with MS who met the ultrasound criteria for CCSVI, and indicated that "Diagnostic venography documented venous obstruction in 100% of the CCSVI-positive patients."

D) Miscellaneous "diagnostic" ultrasound articles related to CCSVI and MS, published since June 2011

The following diagnostic studies of CCSVI and MS used a variety of imaging techniques. The relatively small sample sizes and the "pilot" nature of most of these studies mean that their findings are not definitive. They are included here for completeness.

The study by Bastianello and colleagues (38) is an exception, since they studied 710 patients with MS in six centers (5 Italian and 1 Canadian). The mean age of patients was 45 years, mean EDSS was 4.4 and 55% of patients had relapsing-remitting disease. All ultrasonographers were trained by Zamboni. Overall, they reported that 86% of patients had CCSVI. The frequency of CCSVI varied among centers from a low of 74% to a high of 94%. More striking was the large variation among centers in the proportion of patients who were positive for the individual CCSVI criteria; reflux in the internal jugular and vertebral veins in the sitting and supine position (55% to 94% positive), reflux in the intracranial veins (26% to 91% positive), abnormalities in the internal jugular veins such as stenosis (69% to 89% positive), flow not detectable in the internal jugular and vertebral veins (19% to 46% positive), and reversed postural venous flow (5% to 85% positive). Although one would expect some variation among centers because of differences in patient characteristics, the huge variation among centers for some of the individual CCSVI parameters suggests that there was difficulty standardizing the ultrasound technique and/or subjectivity in interpreting the findings.

Zamboni and colleagues (6) assessed the relationship between the severity of CCSVI (assessed with an ultrasound-based Venous Hemodynamic Insufficiency Severity Score

(VHISS)) and cerebral blood flow (assessed using MRI) in 16 MS patients and 8 age and sex matched controls. There was a statistically significant inverse correlation between VHISS and cerebral blood flow.

Zivadinov and colleagues (39) studied what appear to be the same patients mention in the previous paragraph, and found a positive correlation between the severity of venous abnormalities and iron deposition in the brain, measured by MRI.

Rolf Meyer-Schwickerath and colleagues (40) assessed intracranial venous pressure using ophthalmodynamometry in 29 MS patients and 28 healthy controls, and found no difference in pressure between the two groups.

Monti and colleagues (41) examined differences in cerebral venous outflow under different postural conditions (lying down and sitting up) in MS and controls using ultrasound. Fifty-two MS patients were compared with 27 age- but not gender- matched healthy controls. The ultrasound technique was well described, although the levels chosen for measurement were not entirely clear. Two neuroradiologists who were not blinded to patients vs. control, but who were blinded to MS subtype, evaluated cross sectional area (CSA) of the internal jugular and vertebral veins, and cerebral venous flow. The first 30 patients who were examined independently and blinded showed 86% concordance for results. On the basis of CSA and time average velocity (TAV) for four vessels, the authors calculated the total change in CSA and cerebral venous flow (CVF) defined as TAV*CSA with postural change (erect- seated). CVF change or dCVF was calculated by subtracting supine from erect CVF values. dCVF was reported as positive (dCVF+) or negative (dCVD-). They found 15 IJV stenoses in MS patients but did not provide details. No CSA differences with posture for the IJV in either group were found; vertebral vein measurements were not reported. Comparing the frequency of +dCVF with –dCVF, the authors reported more –dCVF in MS patients compared with controls (60% vs. 4%); i.e. the seated values were higher than the supine values. No differences were observed between relapsing-remitting and secondary progressive MS patients. No correlation was found between –dCVF and stenosis, EDSS, Nine Hole Peg Test, or the timed 8 meter walk test. The results suggest that there is a postural element to CVF, which is maladaptive in patients with MS. However, these changes were not correlated with disability, and there was no difference between patients with relapsing-remitting and secondary progressive disease.

Niggemann and colleagues (42) studied 15 healthy volunteers in an open 0.6T magnet that allowed erect and supine imaging. They used 2D TOF MRV to study vessel visibility and presence of stenoses with posture, while also examining the feasibility of measuring the Zamboni ultrasound criteria objectively with MRI. They demonstrated the postural variation as suggested by Zamboni; where IJV collapses are more common in erect vs. supine position, but also showed that nearly half of the patients did not show IJV changes when erect. Regarding vertebral veins, more were absent when supine but 2 remained absent even when upright. IJV stenoses, arbitrarily defined as >90%, were seen in 8 patients (4 bilateral and 4 unilateral). The authors concluded that they were able to demonstrate several of Zamboni's criteria objectively; including criteria 3, 4, and 5. They

also stated that they could demonstrate reflux by vessel absence on MRV. This point may not be true because the absence of a vessel could be due to collapse or retrograde flow, according to the methodology they used. It is noteworthy that the sequence required 21 minutes which is quite long.

Tanaka and colleagues (43) assessed the cross-sectional area and venous flow of the internal jugular veins in 17 Japanese patients with MS and 11 patients with neuromyelitis optica using ultrasound. The ultrasound technique was poorly described. They found no difference in the cross-sectional area between the two groups of patients. However, venous flow was lowest in the right jugular vein in patients with neuromyelitis optica. The poorly described methods and small sample size make these results difficult to interpret.

E) Studies of endovascular therapy for MS

a) Benefits of endovascular therapy

Randomized trials are widely recognized as the most valid study design to assess the benefits of treatment. This is especially true for a disease like MS which is characterized by spontaneous relapses and remissions, is treated with a number of drugs and other therapies (which can be confounders of the treatment effect), and the likelihood of a placebo effect associated with endovascular treatment.

a-i) Randomized trials

Three randomized trials of endovascular therapy for CCSVI have been registered with clinicaltrials.gov (http://clinicaltrials.gov/ct2/show/NCT01371760?term=CCSVI&rank=8). Two originate in the United States (sample sizes: 130 and 600 patients) and one multi-centre study originates in Italy (sample size: 679 patients). The American studies are currently enrolling patients, but the Italian study has not yet started study recruitment.

One small, non-registered, pseudo-randomized trial of 15 patients with relapsing-remitting MS who were diagnosed with CCSVI has recently been published (12). All patients received venoplasty; no stents were used. They were allocated to receive immediate (8 patients) or delayed venoplasty (7 patients). Patients allocated to the delayed group received venoplasty 6 months later. Patients were recruited from Ferrara Italy and Buffalo USA. Treatment was allocated by “alphabetical order” for Italian patients, and according to whether the patient had a valid passport for American patients.

All patients were followed for 12 months, except for one patient in the delayed group who withdrew from the study at 3 months. Outcomes were evaluated clinically and with ultrasonography at 0, 3, 6, 9 and 12 months. Outcome measures were a) clinical relapse (not defined), b) the MS Functional Composite (MSFC) scale, c) the Expanded Disability Status Scale (EDSS), d) major clinical side-effects, e) re-stenosis on ultrasonography, and f) a number of MS-related MRI outcomes (combined active lesions, gadolinium enhancing lesions, new and active T2 lesions, percent brain volume change, and lateral ventricular volume).

Relapses occurred in one of eight patients in the early group and three of six patients in the delayed group (p=not significant); the total number of relapses was 1 and 5 respectively.

There was no difference in EDSS scores between the two groups. There was an improvement in the MSFC scores compared to baseline in both groups at 6 and 12 months, but no comparison of the two treatment groups with each other was reported. There was an increase in new CAL lesions on MRI in the immediate treatment group, driven by one patient with many lesions. There was a trend towards lower T2 lesion volume in the immediate group at 6 and 12 months, but this was not statistically significant. Overall, no statistically significant differences in MRI findings between the two groups were reported.

a-ii) Non-randomized intervention studies

Non-randomized trials of endovascular treatment are subject to potential biases because of the relapsing-remitting nature of some forms of MS, and the impact of the "placebo effect" on subjective outcomes such as fatigue. Therefore, we place little emphasis upon the reports of such studies. However, for completeness, we briefly describe the four such studies published to date.

Zamboni and colleagues (11) reported on 65 MS patients (35 relapsing remitting, 20 secondary progressive and 10 primary progressive) who underwent endovascular therapy and were followed for up to 18 months (the number of patients actually followed to 18 months is not clear). There was no difference in annualized relapse rates before and after intervention. However, the proportion of patients who were relapse free was 27% before treatment and 50% after treatment. The Multiple Sclerosis Functional Composite Scale improved at 18 months in patients with relapsing-remitting MS, but not in those with progressive MS. The proportion of patients with gadolinium positive lesions decreased from 50% before intervention to 12% afterwards.

Malagoni and colleagues (14) reported on 35 MS patients with CCSVI; it is not clear whether these patients were among the 65 patients in Zamboni's observational study described in the previous paragraph. They assessed fatigue using the Fatigue Severity Scale and the Modified Fatigue Impact Scale at baseline and 1, 6 and 12 months after endovascular therapy. They found significant and persistent improvements in both scales after treatment. They also found improvements in the six minute walk test in those patients who had no lower limb motor impairment.

Ludyga and colleagues (13) reported on 94 MS patients with CCSVI who were evaluated before and six months after endovascular therapy with the Multiple Sclerosis Impact Scale-29, the Fatigue Severity Scale, the Epworth Sleepiness Scale and a 5-point heat intolerance scale. They reported statistically significant improvements in all scales except the heat intolerance scale.

Kostecki and colleagues (15) reported on 36 MS patients with CCSVI who underwent endovascular therapy for internal jugular vein stenosis. Fifteen (42%) were women, mean

age was 38 years, 18 (50%) had relapsing-remitting MS, and the median EDSS was 5.0. One vein was treated in 23 (64%) of patients, while 13 (36%) patients underwent treatment of both internal jugular veins. Stents were inserted in 17 (47%) patients who had no or suboptimal hemodynamic improvement with venoplasty. The mean decrease in vein pressure after treatment was 3.5cm of water on the right and 4.5cm on the left. Patients were treated with "dual anti-platelet" therapy and 2 weeks of low molecular weight heparin. All patients were followed for 6 months, and outcome measures were administered by "independent" neurologists.

No peri-operative treatment complications were reported. At 6 months, restenosis of the treated vein was observed in 12 (33%) patients. There was in-stent restenosis or thrombosis in 10 (59%) of the stents, with total occlusion in 2 patients.

There was no change in median EDSS score or the Epworth Sleepiness Scale during the 6 month follow-up. The Multiple Sclerosis Impact Scale-29 score improved at the three month follow up, but not at 6 months (the mean score decreased from 90 to 73.5). There were improvements at 6 months in the Fatigue Severity Scale (the mean score was 49.5 before treatment and 36 at 6 months) and in the Heat Intolerance Scale (3.5 to 3.0). There was no difference in response at 6 months in patients with and without restenosis (data were not shown).

b) Short-term harms from endovascular therapy

Although the best evidence about the harms of endovascular therapy is derived from randomized trials, well conducted observational studies can provide valid information about the harms associated with a procedure.

We found six studies of endovascular therapy for MS that reported harms of the procedure (11,12,14,37,44,45). One study reported on a subset of patients from a larger study and therefore is not summarized here (14).

Zamboni reported on 65 consecutive MS patients with CCSVI (11). Patients underwent venoplasty, and stents were only inserted in a subset of patients. An attempt was made to conduct a venoplasty on any IJV or azygos vein lesion that had a venous lumen reduction >50% on selective venography. The indications for stent placement were not clearly described, although it appears as if stents were inserted if the IJV was still twisted after venoplasty. All procedures were done in day-surgery with an average post procedure observation period of 4 hours. Patients received prophylactic doses of low molecular weight heparin for 3 weeks post procedure.

The investigators reported no operative or post-operative complications, including vessel rupture, thrombosis, or side-effects to the contrast media. Six patients (9%) complained of headaches that were "transitory and spontaneously resolved". The length of follow-up to assess complications was not reported, but it is likely that only peri-procedure complications were reported.

Ludyga from Poland reported on 564 endovascular procedures in 331 MS patients with CCSVI (44). Venoplasty alone was used in 192 patients and at least one stent was inserted in 152 patients. The discrepancy between the number of patients treated (n=331) and the number of patients with venoplasty alone and at least one stent (n=344) appears to be due to a small number of patients having a repeat procedure, but this is not entirely clear. It is also not clear if all consecutive patients treated by the investigators were reported.

During the procedure, patients received 2500 units of unfractionated heparin. If a stent was inserted, patients received prophylactic doses of low molecular weight heparin for 7 days and 300mg of clopidogrel daily. They then received clopidogrel 75mg daily for 2 months and long term aspirin 125mg daily (it isn't clear whether the aspirin was given with the clopidogrel or started after the clopidogrel was stopped). If no stent was used, patients received prophylactic doses of low molecular dose heparin for 7 days. Neither the length of follow up nor the completeness of follow-up was described.

There were no deaths or strokes. Two patients (1.2%) had stent thrombosis – one immediately and one 2 weeks after the procedure – neither was felt to have clinically important consequences. There were problems with removal of the angioplasty balloon or the delivery system in 5 (1.5%) cases, one of which required opening of the femoral vein. There were no clinical consequences. There were no stent migrations, although 4 stents (2.3% of stentings) moved slightly, requiring the placement of a second stent to secure the first one – all of these occurred when the guide wire was still inside the stent, and there were no clinical consequences. Four (1.2%) patients had to be admitted because of bleeding in the groin; 2 of them developed pseudoaneurysms which required thrombin injection. One patient required admission for a gastrointestinal bleed while on clopidogrel. Two patients (0.6%) developed transient atrial fibrillation during the procedure that was managed medically.

Petrov and colleagues from Sofia, Bulgaria (37) described a retrospective chart review of 461 MS patients with CCSVI who underwent a total of 495 procedures for the treatment of 1012 venous lesions. Thirty four patients underwent re-intervention for re-stenosis (n=11), subacute and chronic thrombosis (n=20) and inadequate initial procedure (n=3). Venoplasty was the preferred procedure, with stents reserved for patients "to treat dilation-resistant lesions, recoil leading to persistent residual venous outflow obstruction, significant and resistant twisting of the vein (especially of the azygous vein), and iatrogenic dissection significantly compromising blood flow". Ninety eight stents were implanted in 76 patients. All patients underwent a post-procedure venogram and an ultrasound the day after the procedure.

Patients received Nadroparin .3ml subcutaneously and aspirin 100mg on the day of the procedure. Intravenous heparin, with a target PTT of 50-70 seconds, was given for 24 hours starting immediately after the procedure. Aspirin 100mg and dabigatran 150 or 75 mg (depending on weight) was given for 3 months after venoplasty and 6 months after stenting.

The focus of Petrov's study was on peri-procedure complications – it appears that follow-up was until the end of the hospitalization for the procedure. Thus, medium to long-term complications were not described. There were no deaths, stroke, myocardial infarction, pulmonary emboli, major hemorrhages or stent migrations. The frequency of headache was not reported. Five patients had groin hematomas that resolved without intervention. Six patients (1.6%) had significant arrhythmias – 4 atrial fibrillation (2 resolved spontaneously, 2 treated with amiodarone), 1 ventricular tachycardia (associated with ST segment elevation) and 1 ventricular fibrillation (previously undiagnosed left main coronary artery disease which was stented during the same hospitalization).

In Petrov's study, mean fluoroscopy time was 23 minutes, with a mean contrast volume of 137ml. There were 2 vein ruptures (both azygos veins, resolved with prolonged balloon inflation and stenting) and 15 limited vein wall dissections (none progressed and stents were inserted in 3). Acute thrombosis occurred within the first 24 hours in 8 procedures (1.6%) – 5 in-stent thrombosis (5% of stents) and 3 in-segment thrombosis (0.3% of dilated veins). All thrombotic lesions were recanalized by selective fibrinolysis, mechanical thromboaspiration or additional balloon venoplasty. One case of vessel recoil was documented on post-procedure ultrasound, and retreated.

In Zamboni's pseudo-randomized trial of 15 patients, one patient had vasovagal syncope 3 hours after venoplasty; otherwise no serious side-effects were reported (12).

Kostecki (15) did not report any serous peri-procedure complications in 36 patients.

Mandato and colleagues (45) reported a retrospective study of 257 endovascular procedures on 240 consecutive patients in Albany USA. Forty-nine percent of patients were treated in hospital and 51% as outpatients. Primary procedures accounted for 93% and repeat interventions for 7% of procedures. Stents were inserted in 11% of the primary procedures and 50% of the repeat procedures. Patients who underwent venoplasty were placed on aspirin, and patients receiving stents were placed on clopidogrel for 6 months, followed by aspirin. "Most" patients had an ultrasound 24 hours after the procedure. The mean age of patients was 49 years, 65% were female and 62% had relapsing-remiting MS. All patients were followed for one month after the procedure.

Headache was reported in 9% of patients, and transient neck pain in 15%. Three patients (1.2%) had thrombosis of the internal jugular vein within 30 days of the procedure; 2 were discovered on the routine ultrasound 24 hours after the procedure, the third was discovered when a patient's MS symptoms worsened and an ultrasound was done. Sustained cardiac arrhythmias occurred in 3 (1.2%) of patients; two required hospital admission and one patient developed severely depressed left ventricular systolic function during attempted stent recanalization. She required intubation and inotropic support and was diagmosed with stress-induced (takotsubo) cardiomyopathy. Her ventricular function recovered well, she was discharged after 4 days, and she had no significant sequellae 90 days later.

c) Long-term harms of endovascular therapy
Mandato's study (45) followed patients for a month after endovascular therapy; he found no serious complications after patients were discharged. However, serious medium to long term complications such as death, pulmonary embolism, stent migration, serious hemorrhage and thrombosis of the internal jugular vein requiring thrombectomy have been reported (46-49). More studies with long-term follow-up after endovascular therapy are needed.

d) Re-stenosis after endovascular therapy
Zamboni's protocol called for ultrasonography at 3, 6, 12, 15 and 18 months after initial treatment (11). At 18 months, all patients with suspected re-stenosis were to undergo repeat venography. He reported a stenosis-free survival at 18 months of 96% in the azygos veins, compared with 53% in the IJVs. However, Zamboni did not report the number of patients evaluated at each interval, or the number of patients lost to follow up. He reported that 100% of patients with suspected re-stenosis on ultrasonography had re-stenosis confirmed with venography at 18 months, but he did not indicate how many patients underwent repeat venography.

Zamboni also reported re-stenosis rates in his trial of 15 patients who were followed for 6 to 12 months (one patient lost to follow-up) (12). No re-stenoses were reported in ayzgous veins. Re-stenosis in the IJV occurred in one patient (12.5%) in the immediate group at 12 months, and in three patients (50%) in the delayed group (two occurred three months after venoplasty and one occurred 6 months after venoplasty). The restenosis rate in both groups combined was 4/14 (29%).

At 6 months, Kostecki (15) reported restenosis of the treated vein in 12 (33%) patients. There was in-stent restenosis or thrombosis in 10 (59%) of the stents, with total occlusion in 2 patients.

DISCUSSION

Studies of Doppler ultrasonography
The most striking result of our meta-analysis of ten studies that used Doppler ultrasonography to evaluate the frequency of CCSVI in patients with MS compared with healthy controls or patients with other neurological diseases was the large variation in the frequency of CCSVI in patients with MS, which ranged from 100% to 0%. Although there was a large, statistically significant association between CCSVI and multiple sclerosis when compared to healthy controls, the large amount of heterogeneity among the individual studies' results do not allow definitive conclusions to be drawn.

The cause of the heterogeneity is not clear. It may be that the ultrasound technique varied among studies. Interestingly, even in a six centre study of 710 MS patients (5 Italian and 1 Canadian centers) in which all ultrasonographers were trained by Zamboni, there were large variations in the frequency with which individual CCSVI parameters were abnormal (e.g. reflux in the intracranial veins was diagnosed in 26% of patients in one centre and 91% in another; reverted postural control was found in 5% of patients in one

centre and 86% in another) (38). There is an urgent need to agree upon a standardized method of diagnosing CCSVI and training ultrasonographers, so there is better agreement among ultrasonographers. We note that a consensus document about how to screen for CCSVI was developed at the first meeting of the newly established International Society for Neurovascular Disease in March 2011, which has been submitted for publication (50).

Blinding of the persons conducting and interpreting the ultrasound is important. Some studies were unblinded, while others described themselves as blinded (although the quality of the description of the blinding varied among studies). None of the studies reported the success of blinding. Although the blinding status of the studies did not appear correlated with the results of the studies, it is important that all future studies are carefully blinded and report the success of blinding.

A number of studies are currently underway evaluating the association of CCSVI with MS. We note in particular a blinded, multicentre Italian study which plans to enroll 1200 patients with MS, 400 healthy controls and 400 patients with other neurological diseases (http://clinicaltrials.gov/ct2/show/NCT01384825?term=CCSVI&rank=3). The estimated date of completion is February 2012, and if completed as planned, this study will be by far the largest study of the association between CCSVI and MS.

Studies of magnetic resonance venography

There were only three studies assessing MRV in MS patients and non-MS controls. None found any statistically significant differences between MS patients and controls, but the sample sizes were so small (a total of 98 patients with MS), and the MRV methods sufficiently different, that it is not possible to make any conclusions about whether there are differences in MRV findings between MS patients and individuals without MS.

Studies of contrast venography

One high quality but small study reported venographic findings in a relatively unselected group of MS patients (36). Yamout found an increase in the frequency of extracranial venous stenoses according to the length of time that patients had MS: 9% in patients with clinically isolated syndrome, 33% in patients with early relapsing remitting MS and 85% in patients with late MS. There was no description of blinding, so the investigator appears to have been aware of the clinical diagnosis of the patients. These results argue against venous stenosis being the cause of MS, but the finding of abnormalities in 85% of individuals who had MS for many years raises the question of whether long-standing MS might be the cause of the venous abnormalities. We noted that a recent study by Bastianello found that CCSVI was more frequently diagnosed in patients with progressive MS than relapsing-remitting MS (38).

The results of the five studies of MS patients with CCSVI diagnosed by ultrasonography, three of which were very small, found a large difference in the frequency of abnormalities on venography, ranging from 14% to 100%. More studies are clearly needed.

Effectiveness of endovascular treatment of CCSVI

Four non-controlled before-after studies have reported on the effect of endovascular therapy on patient outcomes and MRI findings, and all reported some improvements after treatment. However, no randomized trials or observational studies with control groups have been reported. Therefore, one cannot make reliable conclusions about the benefits of endovascular treatment. Restenosis after treatment occurs in a significant number (between 29% and 47%) of patients, 6 to 18 months after endovascular therapy.

Short-term harms of endovascular treatment of CCSVI

Five studies have reported on the short-term harms of endovascular treatment of CCSVI, in a total of 1148 patients. There were no deaths, and the treatment was in general well-tolerated. The most frequent serious side-effect was cardiac arrhythmia, which occurred in 1 to 2 percent of patients; one patient developed a stress-induced cardiomyopathy at the time of the arrhythmia from which she recovered. .

Medium to long-term harms of endovascular treatment for CCSVI

Serious complications such as stent migration, major hemorrhage, pulmonary embolism, internal jugular vein thrombosis requiring thrombectomy and death have occurred after endovascular therapy (46-49). However, only one study (45) has described the harms of endovascular treatment after the immediate peri-procedure period in a cohort of patients; patients were followed for one month in that study. Therefore, we know little about the frequency of these complications, and more studies are clearly needed.

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Table 1: Characteristics of studies included in the meta-analysis that compared the frequency of chronic cerebrospinal venous insufficiency among patients with and without multiple sclerosis (MS)

Study	No. of patients with MS	No. of controls		Ultrasound equipment used	Blinding
		Healthy controls	Patients with other neurological diseases		
Al-Omari et al.	25	25	N/A	Philips ATL HDI 5000 4-7MHz linear probe and/or 5-8Mhz curved probe, Transcranial Doppler not performed (probe not available).	Not blinded.
Baracchini et al.	50	110	60	Philips iU22 Extracranial: 5-10 MHz linear array probe. Transcranial: 1-3 MHz phased array probe.	Described as blinded but did not describe how blinding ensured or whether blinding tested.
Centonze et al.	84	56	N/A	Esaote Biomedica MyLab-Vinco 25 with a linear LA322 11-3 MHz probe.	Described blinding process but did not describe whether blinding achieved.
Doepp et al.	56	20	N/A	Toshiba Powervision 6000, Extracranial exam: 7.5MHz linear transducer. Transcranial exam: 2.5MHz probe.	Not blinded.
Krogias et al.	10	2	5	Not described.	Not blinded.
Mayer et al.	20	20	N/A	Phillips IU22 with an L9-3 probe to assess IJV and VV; S5-1 probe was used for intracranial veins.	Described blinding process but did not describe whether blinding achieved.
Zamboni et al.	109	132	45	Esoate-Biosound My lab 25 7.5-10 MHz for extracranial, 2.5 MHz for intracranial.	Described as blinded but did not describe how blinding undertaken or whether

					blinding achieved.
Zivadinov et al.	310	163	26	Esaote-Biosound MyLabGOLD25 equipped with 2.5 and 7.5-10 MHz transducers.	Described blinding process but did not describe whether blinding achieved.
Marder et al.	18	N/A	11	Logic 9, GE Healthcare 8MHz linear array probe for extracranial; 2-MHz sector transducer for transcranial examination.	Described as blinded but did not describe how blinding ensured or whether blinding tested.
Baracchini et al.	60	60	N/A	Phillips IU22 with a 5-10 MHz linear probe for extracranial and 1-3 MHz phased-array TCD for intracranial veins.	Described blinding process but did not assess the effectiveness of blinding.

Note: MS = multiple sclerosis patients, HC = healthy controls, OND = patients with other neurological diseases, N/A = not applicable.
Study references, in order of appearance in table: (17), (18), (19), (20), (21), (22), (3), (23), (25), (24).

Table 2: Characteristics of patients with multiple sclerosis (MS) included in studies

Study	Type of MS; no. of MS patients			Age, yr	Female, %	EDSS score	Use of disease-modifying medications, %	Duration of MS, yr
	Clinically isolated syndrome	Relapsing-remitting	Other					
Al-Omari et al.	0	21	4	35*	52	N/A	N/A	N/A
Baracchini et al.	50	0	0	33*	70	1.5†	28	N/A
Centonze et al.	0	69	15	39*	62	N/A	82	N/A
Doepp et al.	0	41	15	42*	65	2.7*	N/A	10*
Krogias et al.	0	2	8	42†	30	5.8†	N/A	N/A
Mayer et al.	0	17	3	42*	65	3†	90	13*
Zamboni et al.	0	69	40	40†	59	2†	N/A	6†
Zivadinov et al.	21	191	98	48†	76	3†	89‡	12†
Marder et al.	1	6	11	55*	17	N/A	N/A	21†
Baracchini et al.								
1° progressive	0	0	25	47*	44	6*	N/A	11*
2° progressive	0	0	35	45*	63	6*	N/A	18*

Note: EDSS = Expanded Disability Status Scale, N/A = information not available. * = mean. † = median.
‡ = calculation based on N=289 MS patients (without CIS subgroup).
Study references for studies, in order of appearance in table: (17), (18), (19), (20), (21), (22), (3), (23), (25), (24).

Table 3: Characteristics of participants included in the control groups

Study	No. of participants	Age, yr	Female, %
Healthy controls			
Al Omari et al.	25	34‡	52
Baracchini et al.			
Group 1*	50	33‡	70
Group 2†	60	63‡	53
Centonze et al.	56	42‡	64
Doepp et al.	20	41‡	60
Mayer et al.	20	34‡	50
Zamboni et al.			
Group 1*	60	37§	53
Group 2†	72	58§	60
Zivadinov et al.	163	47§	54
Baracchini et al.	60	46‡	55
Controls with other neurological diseases			
Baracchini et al.	60	64‡	53
Krogias et al.	7	40§	29
Zamboni et al.	45	60§	44
Zivadinov et al.	26	50§	73
Marder et al. ◊	11	55‡	36

Note: MS = multiple sclerosis, NA = not applicable. ‡Mean. §Median.
*Healthy controls in group 1 were matched with MS patients.
†In the study by Baracchini et al., healthy controls in group 2 were matched with controls who had neurologic diseases other than MS; in the study by Zamboni et al., healthy controls in group 2 were older than the median age of the European MS population.
◊ Controls with other neurological diseases in the study by Marder et al. were composed of individuals with migraine headaches as well as individuals without a neurological diagnosis (i.e. healthy controls).

Study references, in order of appearance in table: (17), (18), (19), (20), (22), (3), (23), (24), (18) (21), (3), (23), (25).

Table 4: Methodological quality of studies included in meta-analysis*

Study	Experience level		Case definition		Representativeness of patients	
	Was evidence provided that the operator has adequate experience to conduct the test?	Was evidence provided that the interpreter has adequate experience to interpret results?	Were MS patients examined to confirm that they had MS?	Were controls examined to confirm that they did not have MS or to confirm other neurological diagnosis?	How were patients identified for enrolment?	Were controls matched to cases by sex and age?
Al-Omari et al.	No	No	Not sure	No	Convenience	Yes
Baracchini et al.	No	No	Yes	No	Consecutively	Yes
Centonze et al.	Yes	Yes	Yes	No	Convenience	Yes
Doepp et al.	No	No	Yes	No	Convenience	Yes
Krogias et al.	No	No	Not sure	No	Convenience	Not sure
Mayer et al.	No	No	Not sure	No	Convenience	No
Zamboni et al.	Yes	Yes	Not sure	No	Convenience	Yes
Zivadinov et al.	Yes	Yes	Yes	Yes	Convenience	No
Marder et al.	No	No	Not sure	No	Convenience	Yes
Baracchini et al.	No	No	Yes	No	Consecutively	Yes

Note: MS = multiple sclerosis.

*Methodological quality was assessed using items derived from the Newcastle–Ottawa Quality Assessment Scale tool for observational studies.

Study references, in order of appearance in table: (17), (18), (19), (20), (21), (22), (3), (23), (25), (24).

Table 5. Characteristics of the eligible studies examining magnetic resonance venography (MRV) in patients with MS and healthy controls

First author & publication year, funding source	Setting	Recruitment	Equipment	Blinding of investigators	Representativeness of MS patients
Sundstrom, P., et al., 2010. *Funding*: unknown	Umea, Sweden	MS clinic	MRI 3TPhilips, 8 channel – 3D FFE CE MRA head/neck – Matrix, no FOV/ST –T2 3mm, 1mm FLAIR and T1 post C – PC MRA/V/CSF-ICA,VA,IJV venc 70, csf venc 20, 5-6mm ST, matrix/FOV given	Information not provided, suspect not blinded	Convenience sample
Wattjes, M.P. et al., 2011. *Funding:* Dutch foundation for MS research	Amsterdam, Netherlands	MS outpatient clinic	MRI 3T (Signa HDXt, 8 channel coil) (matrix/FOV given) – 2D PD/T2 FSE 3mm, – 3D FLAIR 1.2mm – 2D T1 3mm post C – MRV 3D PC1.4mm venc 15cm/s – 3d CEMRA 3mm – 2d PC perpendicular to ICV/SS (blinded reader) – Only assessed ICV, StrS – Cardiac gated	Blinded	Convenience sample
Zivadinov, R., et	Buffalo, NY,	MS clinic	3T MRI, 8 channel	MR image interpreters	Consecutive patients

al., 2011. *Funding*: unknown	USA	– TOF ST 1.5*0.7*1.1mm (No mention of saturation band presence- images suggest not) – TRICKS 2*1.1*1.8mm – Omniscan 20cc/ 20cc saline, 2ml/s	blinded, not sure about those who conducted the test

Study references, in order of appearance in table: (30), (31), (32).

Table 6. Characteristics of the patients in the eligible studies examining magnetic resonance venography (MRV) in patients with MS and healthy controls

Sundstrom 2010	**MS patients**				**Control patients**		
	Tot	RR	PP	SP	Tot	Healthy	OND
N	21				20		
Age (median)	31				31		
Sex (F:M)	13:8				8:12		
EDSS (median)	2.0						
Length of MS (years, median)	5						
Disease-modifying drugs (Y:N)	16:5						
Exclusion Criteria	None.						
Wattjes 2010	**MS patients**				**Control patients**		
	Tot	RR	PP	SP	Tot	Healthy	OND
N	20	19	1		20		
Age (mean)	35				35		
Sex (F:M)	15:5				15:5		
EDSS (median)	2.25						
Length of MS (years, mean)	9						
Disease-modifying drugs (Y:N)	14:6						
Exclusion Criteria	Other immunological or malignant diseases, pregnancy, contraindication to MRI, allergic reaction to dye, impaired renal function.						
Notes	Controls: age- and sex-matched with MS patients.						

Zivadinov 2011	**MS patients**				**Control patients**		
	Tot	RR	PP	SP	Tot	Healthy	OND
N	57	41		16		21	
Age (mean)	45					43	
Sex (F:M)	40:17					14:7	
EDSS (median)	2.5						
Length of MS (years, mean)	13						
Disease-modifying drugs (Y:N)	49:8						
Exclusion Criteria	Relapse and steroid treatment in last 30 days, cerebral congenital vascular malformations, contraindication to contrast, pregnancy, conditions known to be associated with pathological abnormalities of the neck.						
Notes	Controls: age- and sex-matched with MS patients.						

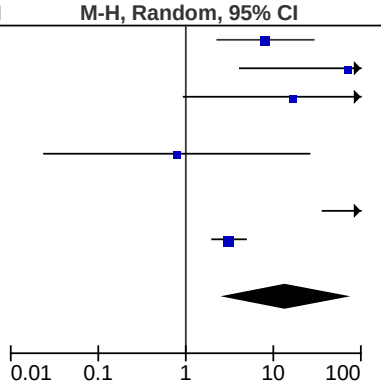
Note: RR = relapse-remitting MS, PP = primary progressive MS, SP = secondary progressive MS, OND = other neurological diseases.

Study references, in order of appearance in table: (30), (31), (32).

CCSVI Parameter 1

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Omari	18	25	6	25	21.2%	8.14 [2.29, 28.90]
Baracchini i	12	50	0	110	14.4%	71.75 [4.15, 1240.95]
Baracchini ii	7	60	0	60	14.2%	16.96 [0.95, 304.07]
Doepp	0	56	0	20		Not estimable
Krogias	1	10	0	2	12.0%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Zamboni	76	109	0	132	14.5%	605.15 [36.56, 10016.99]
Zivadinov	137	310	33	163	23.7%	3.12 [2.00, 4.86]
Total (95% CI)		**640**		**532**	**100.0%**	**13.94 [2.54, 76.49]**
Total events	251		39			

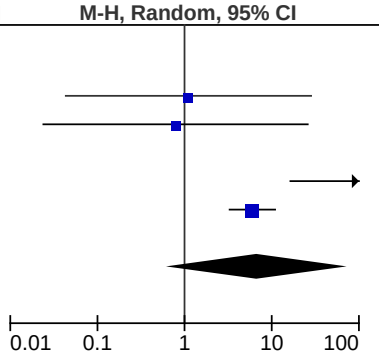
Heterogeneity: Tau² = 3.14; Chi² = 27.79, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.03 (P = 0.002)



CCSVI Parameter 2

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	0	50	0	110		Not estimable
Baracchini ii	0	60	0	60		Not estimable
Doepp	1	56	0	20	21.4%	1.11 [0.04, 28.31]
Krogias	1	10	0	2	20.2%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Zamboni	55	109	0	132	23.8%	269.86 [16.38, 4447.00]
Zivadinov	110	236	15	118	34.6%	5.99 [3.29, 10.91]
Total (95% CI)		**541**		**462**	**100.0%**	**6.86 [0.63, 74.90]**
Total events	167		15			

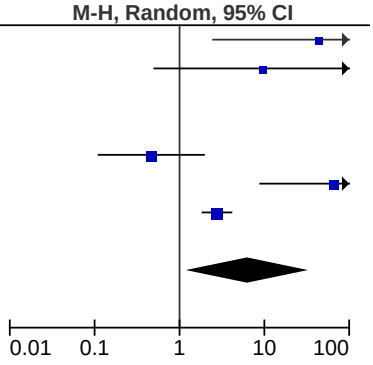
Heterogeneity: Tau² = 4.20; Chi² = 12.18, df = 3 (P = 0.007); I² = 75%
Test for overall effect: Z = 1.58 (P = 0.11)



CCSVI Parameter 3

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	0	110	15.1%	44.20 [2.50, 782.70]
Baracchini ii	4	60	0	60	14.8%	9.64 [0.51, 183.05]
Doepp	0	56	0	20		Not estimable
Krogias	0	10	0	2		Not estimable
Mayer	13	20	16	20	23.0%	0.46 [0.11, 1.94]
Zamboni	30	109	1	177	19.7%	66.84 [8.96, 498.80]
Zivadinov	197	310	63	163	27.3%	2.77 [1.87, 4.09]
Total (95% CI)		**615**		**552**	**100.0%**	**6.29 [1.20, 33.12]**
Total events	252		80			

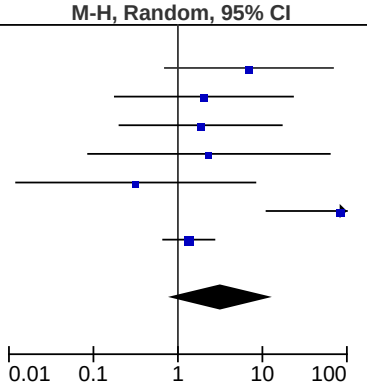
Heterogeneity: Tau² = 2.59; Chi² = 21.66, df = 4 (P = 0.0002); I² = 82%
Test for overall effect: Z = 2.17 (P = 0.03)



CCSVI Parameter 4

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Omari	0	25	0	25		Not estimable
Baracchini i	3	50	1	110	14.2%	6.96 [0.71, 68.63]
Baracchini ii	2	60	1	60	13.6%	2.03 [0.18, 23.06]
Doepp	5	56	1	20	14.6%	1.86 [0.20, 16.99]
Krogias	3	10	0	2	10.2%	2.33 [0.09, 62.68]
Mayer	0	20	1	20	10.3%	0.32 [0.01, 8.26]
Zamboni	35	109	1	177	15.6%	83.24 [11.20, 618.93]
Zivadinov	30	310	12	163	21.4%	1.35 [0.67, 2.71]
Total (95% CI)		**640**		**577**	**100.0%**	**3.27 [0.79, 13.55]**
Total events	78		17			

Heterogeneity: Tau² = 2.33; Chi² = 20.42, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 1.63 (P = 0.10)



CCSVI Parameter 5

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Omari	4	25	0	25	7.5%	10.67 [0.54, 209.64]
Baracchini i	8	50	6	110	18.5%	3.30 [1.08, 10.09]
Baracchini ii	4	60	3	60	15.2%	1.36 [0.29, 6.34]
Doepp	4	56	3	20	14.8%	0.44 [0.09, 2.15]
Mayer	0	20	0	20		Not estimable
Zamboni	61	109	21	177	22.4%	9.44 [5.22, 17.07]
Zivadinov	35	310	11	163	21.7%	1.76 [0.87, 3.56]
Total (95% CI)		**630**		**575**	**100.0%**	**2.58 [0.97, 6.84]**
Total events	116		44			

Heterogeneity: Tau² = 1.02; Chi² = 22.95, df = 5 (P = 0.0003); I² = 78%
Test for overall effect: Z = 1.90 (P = 0.06)

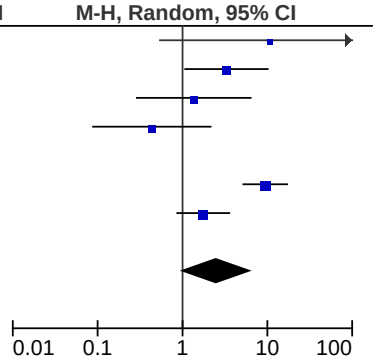


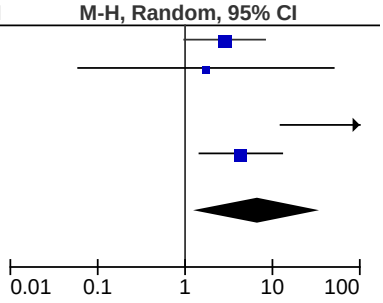
Figure 3: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus healthy controls (HC). (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (4) flow not detectable in internal jugular veins or vertebral veins; and (5) reverted postural control of main cerebral venous outflow pathway (internal jugular veins). An odds ratio greater than 1.0 indicates an increased likelihood of the parameter being present in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari (17), Baracchini i (18), Baracchini ii (24), Centonze (19), Doepp (20), Krogias (21), Mayer (22), Zamboni (3), Zivadinov (23).

CCSVI Parameter 1

Study or Subgroup	MS Events	MS Total	OND Events	OND Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	12	50	6	60	33.5%	2.84 [0.98, 8.24]
Krogias	1	10	0	5	14.9%	1.74 [0.06, 50.43]
Marder	0	18	0	11		Not estimable
Zamboni	76	109	0	45	18.3%	207.81 [12.43, 3473.88]
Zivadinov	137	310	4	26	33.3%	4.36 [1.47, 12.94]
Total (95% CI)		**497**		**147**	**100.0%**	**6.67 [1.28, 34.82]**
Total events	226		10			

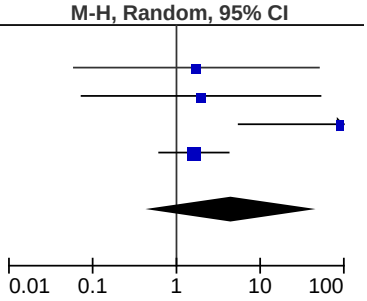
Heterogeneity: Tau² = 1.82; Chi² = 11.13, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 2.25 (P = 0.02)



CCSVI Parameter 2

Study or Subgroup	MS Events	MS Total	OND Events	OND Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	0	50	0	60		Not estimable
Krogias	1	10	0	5	20.7%	1.74 [0.06, 50.43]
Marder	1	18	0	11	21.2%	1.97 [0.07, 52.70]
Zamboni	55	109	0	45	23.8%	92.67 [5.57, 1542.24]
Zivadinov	110	236	7	20	34.2%	1.62 [0.62, 4.21]
Total (95% CI)		**423**		**141**	**100.0%**	**4.50 [0.43, 46.82]**
Total events	167		7			

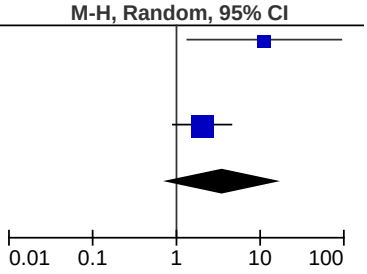
Heterogeneity: Tau² = 3.94; Chi² = 10.93, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.26 (P = 0.21)



CCSVI Parameter 3

Study or Subgroup	MS Events	MS Total	OND Events	OND Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	1	60	33.6%	11.24 [1.35, 93.27]
Krogias	0	10	0	5		Not estimable
Marder	0	18	0	11		Not estimable
Zivadinov	197	310	12	26	66.4%	2.03 [0.91, 4.55]
Total (95% CI)		**388**		**102**	**100.0%**	**3.61 [0.72, 18.14]**
Total events	205		13			

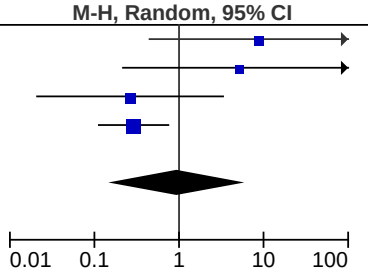
Heterogeneity: Tau² = 0.85; Chi² = 2.28, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 1.56 (P = 0.12)



CCSVI Parameter 4

Study or Subgroup	MS Events	MS Total	OND Events	OND Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	3	50	0	60	20.0%	8.92 [0.45, 176.84]
Krogias	3	10	0	5	18.8%	5.13 [0.22, 121.10]
Marder	1	18	2	11	23.5%	0.26 [0.02, 3.33]
Zivadinov	30	310	7	26	37.7%	0.29 [0.11, 0.75]
Total (95% CI)		**388**		**102**	**100.0%**	**0.97 [0.15, 6.18]**
Total events	37		9			

Heterogeneity: $Tau^2 = 2.14$; $Chi^2 = 8.03$, df = 3 (P = 0.05); $I^2 = 63\%$
Test for overall effect: Z = 0.03 (P = 0.97)



CCSVI Parameter 5

Study or Subgroup	MS Events	MS Total	OND Events	OND Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	6	60	49.7%	1.71 [0.55, 5.32]
Krogias	1	10	1	7	7.3%	0.67 [0.03, 12.84]
Marder	2	18	2	11	14.1%	0.56 [0.07, 4.70]
Zivadinov	35	310	2	26	28.9%	1.53 [0.35, 6.74]
Total (95% CI)		**388**		**104**	**100.0%**	**1.32 [0.60, 2.94]**
Total events	46		11			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.07$, df = 3 (P = 0.79); $I^2 = 0\%$
Test for overall effect: Z = 0.69 (P = 0.49)

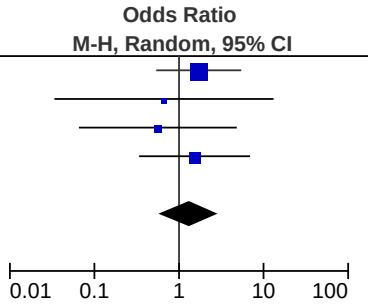
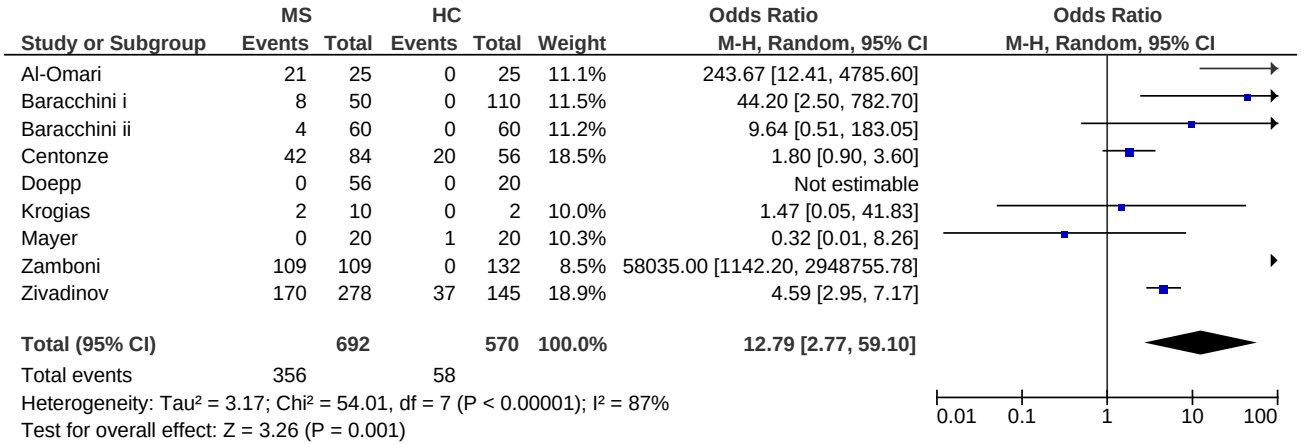


Figure 4: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus controls with other neurological diseases (OND). (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (4) flow not detectable in internal jugular veins or vertebral veins; and (5) reverted postural control of main cerebral venous outflow pathway (internal jugular veins). An odds ratio greater than 1.0 indicates an increased likelihood of the parameter being present in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Baracchini i (18), Krogias (21), Marder (25), Zamboni (3), Zivadinov (23).



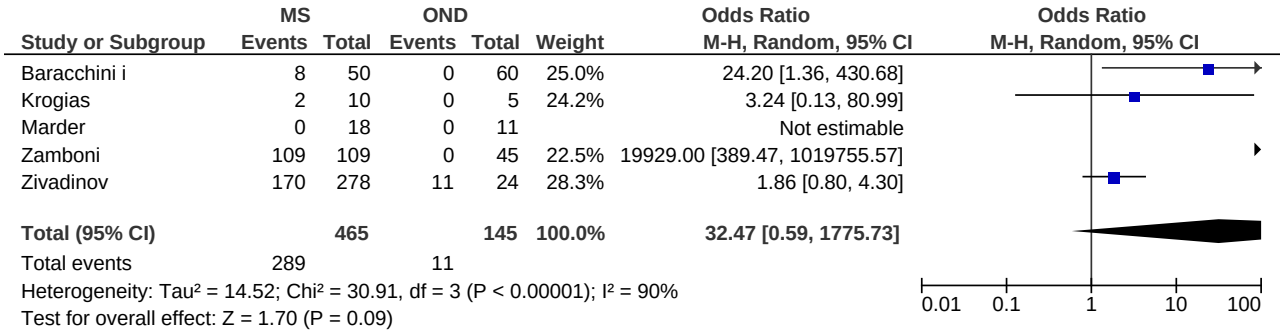
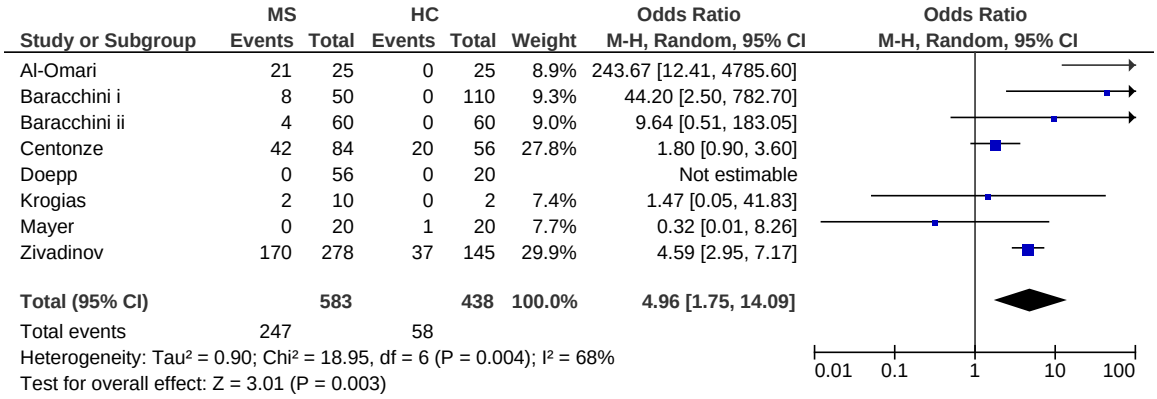


Figure 5: Meta-analysis of a diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (HC) (top panel) and controls with other neurological diseases (OND) (bottom panel). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari (17), Baracchini i (18), Baracchini ii (24), Centonze (19), Doepp (20), Krogias (21), Marder (25), Mayer (22), Zamboni (3), Zivadinov (23).



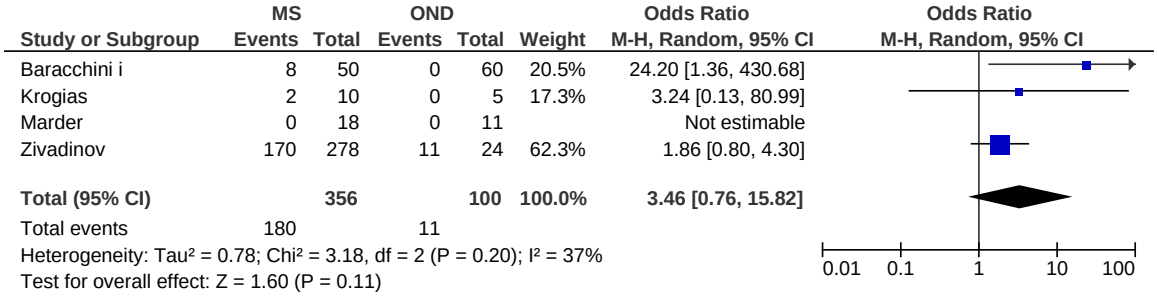


Figure 6: Sensitivity analysis of a diagnosis of chronic cerebrospinal venous insufficiency in patients with MS versus healthy controls (HC) (top panel) and controls with other neurological diseases (OND) (bottom panel), with study by Zamboni et al. removed. An odds ration greater than 1.0 indicates increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari (17), Baracchini i (18), Baracchini ii (24), Centonze (19), Doepp (20), Krogias (21), Marder (25), Mayer (22), Zivadinov (23).

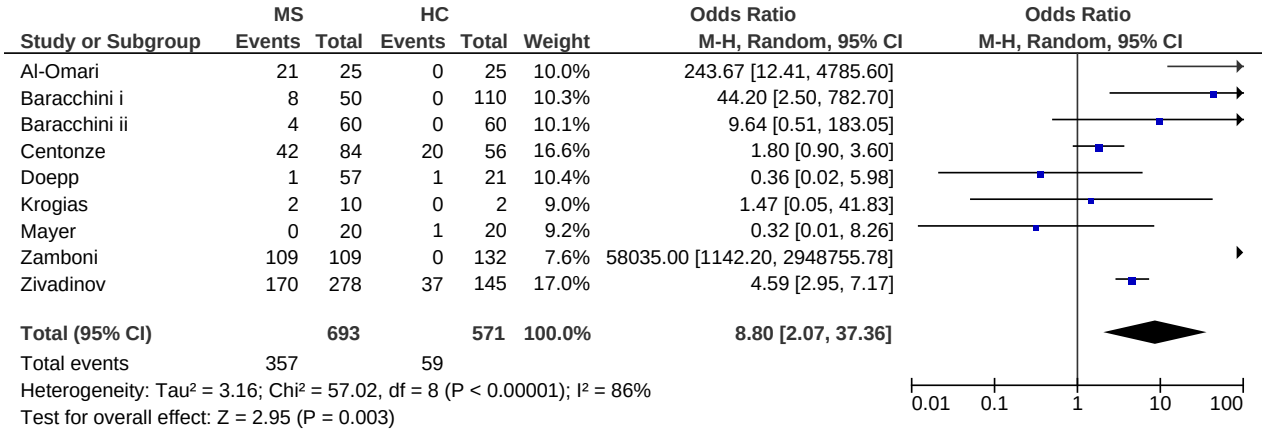


Figure 7: Sensitivity analysis of a diagnosis of chronic cerebrospinal venous insufficiency in patients with MS versus healthy controls, with study by Doepp et al. included (1 added to each cell). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari (17), Baracchini i (18), Baracchini ii (24), Centonze (19), Doepp (20), Krogias (21), Mayer (22), Zamboni (3), Zivadinov (23).

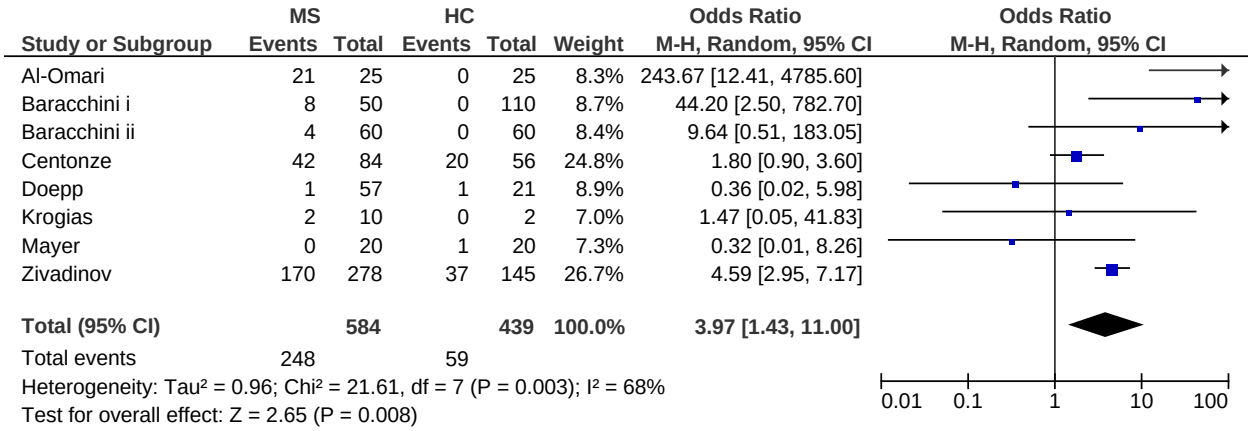


Figure 8: Sensitivity analysis of a diagnosis of chronic cerebrospinal venous insufficiency in patients with MS versus healthy controls, with study by Zamboni et al. removed and study by Doepp et al. included (1 added to each cell). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari (17), Baracchini i (18), Baracchini ii (24), Centonze (19), Doepp (20), Krogias (21), Mayer (22), Zivadinov (23).

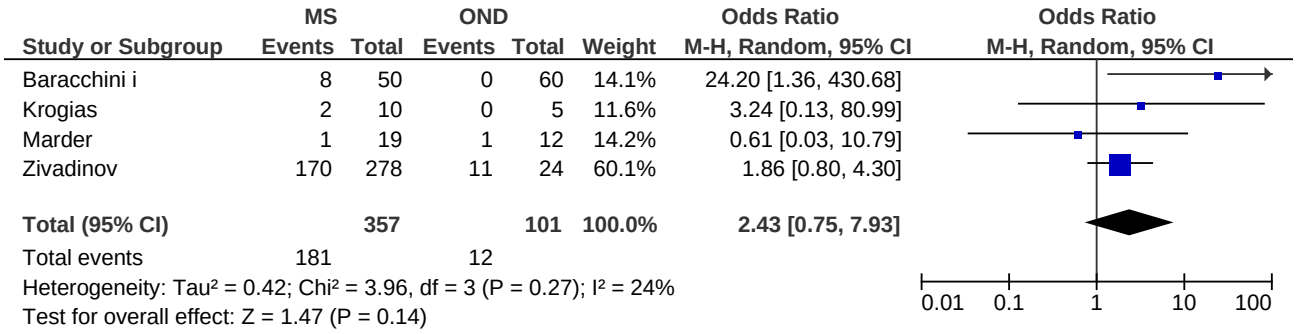


Figure 9: Sensitivity analysis of a diagnosis of chronic cerebrospinal venous insufficiency in patients with MS versus controls with other neurological diseases (OND), with study by Zamboni et al. removed and study by Marder et al. included (1 added to each cell). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Baracchini i (18), Krogias (21), Marder (25), Zivadinov (23).

APPENDIX – LITERATURE SEARCH STRATEGIES

MEDLINE Search Strategy, Studies of Association

1 Multiple Sclerosis/
2 Multiple Sclerosis, Chronic Progressive/
3 Multiple Sclerosis, Relapsing-Remitting/
4 (multiple adj sclerosis).mp.
5 Neuromyelitis Optica/
6 (neuromyelitis adj optica).mp.
7 Myelitis, Transverse/
8 (transverse adj myelitis).mp.
9 Demyelinating Diseases/
10 (demyelinating adj (disease? or disorder?)).mp.
11 Encephalomyelitis, Acute Disseminated/
12 ADEM.tw.
13 encephalomyelitis.tw.
14 Optic Neuritis/
15 (optic adj neuriti$).mp.
16 devic.tw.
17 "clinically isolated syndrome?".tw.
18 or/1-17

19 exp Ultrasonography/ [Diagnostic]
20 ultrasonogra$.mp.
21 ultrasound$.tw.
22 Doppler$.mp.
23 Phlebography/
24 phlebogra$.mp.
25 venogra$.mp.
26 Magnetic Resonance Angiography/
27 "magnetic resonance angiogra$".tw.
28 "magnetic resonance arteriogra$".tw.
29 Cerebral Angiography/
30 (cerebral adj angiogra$).tw.
31 (cerebral adj arteriogra$).tw.
32 (venous adj angiogra$).tw.
33 (venous adj arteriogra$).tw.
34 (brain adj angiogra$).tw.
35 (brain adj arteriogra$).tw.
36 or/19-35

37 18 and 36
38 Animals/ not (Animals/ and Humans/)
39 37 not 38
40 limit 39 to yr="2005 -Current"

MEDLINE Search Strategy, Studies of Treatment

1 Multiple Sclerosis/ (33498)
2 Multiple Sclerosis, Chronic Progressive/ (1015)
3 Multiple Sclerosis, Relapsing-Remitting/ (2360)
4 (multiple adj sclerosis).mp. (44528)
5 Neuromyelitis Optica/ (704)
6 (neuromyelitis adj optica).mp. (927)
7 Myelitis, Transverse/ (864)
8 (transverse adj myelitis).mp. (1016)
9 Demyelinating Diseases/ (8797)
10 (demyelinating adj disease?).mp. (11563)
11 Encephalomyelitis, Acute Disseminated/ (1307)
12 ADEM.tw. (414)
13 encephalomyelitis.tw. (12019)
14 Optic Neuritis/ (4261)
15 (optic adj neuritis).mp. (5225)
16 devic.tw. (85)
17 or/1-16 (65502)

18 exp Angioplasty/ [Treatment] (46449)
19 angioplasty.mp. (55724)
20 exp Cerebrovascular Disorders/ (230419)
21 (cerebrovascular adj disorder?).mp. (41935)
22 exp Stents/ (40377)
23 stent$.tw. (47736)
24 exp Vascular Surgical Procedures/ (155384)
25 (endovascular adj (therap$ or treatment? or procedure?)).tw. (6497)
26 venoplast$.tw. (171)
27 Jugular Veins/ (8867)
28 (jugular adj vein?).tw. (9717)
29 exp Balloon Dilation/ (53922)
30 (balloon adj dilation?).mp. (13885)
31 "chronic cerebrospinal venous insufficienc$".tw. (42)
32 CCSVI.tw. (33)
33 or/18-32 (427988)

34 17 and 33 (1806)
35 Animals/ not (Animals/ and Humans/) (3471083)
36 34 not 35 (1758)
37 limit 36 to yr="2005 - Current" (434)