

**Systematic reviews of the evidence regarding chronic cerebral spinal venous
insufficiency (CCSVI) and multiple sclerosis
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Andreas Laupacis, MD, MSc^{1,2}
Erin Lillie MSc¹
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, MSc⁶
Kevin Thorpe, MMath^{1,7}
Thomas Feasby, MD⁸
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

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). The primary purpose of this systematic review was to examine the evidence evaluating the association between venous abnormalities and MS. The secondary purpose was to systematically review the current evidence about the benefits and harms of endovascular treatment for MS.

Methods: Studies assessing ultrasound and magnetic resonance venography (MRV) were eligible if they compared MS patients with patients without MS [either healthy controls (HC) or patients with other neurological diseases (OND)]. Because of the side-effects of contrast venography (CV), it would not be appropriate to expose control patients to CV. Therefore, CV studies were eligible even if they did not have a non-MS control group. Only randomized trials were eligible for the assessment of the benefits of endovascular treatment for MS. To assess the harms of endovascular treatment, we accepted 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: 8 studies compared the frequency of CCSVI diagnosed with ultrasound in MS patients with HC, and 4 studies compared MS patients with OND. CCSVI was diagnosed more frequently in patients with MS than in HC [odds ratio (OR) 13.53, $p=0.002$], 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 3.68, $p=0.02$). The 4 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 32.47, $p=0.09$); removal of Zamboni's study resulted in an OR of 3.7, $p=0.10$. None of the studies using ultrasound reported the success of blinding of the technicians or radiologists. Only 3 small studies evaluated MRV findings in patients with MS and HC, and they found no statistically significant differences. 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.

No randomized trials have been reported of endovascular therapy for MS; therefore the impact of this intervention upon the symptoms and signs of MS cannot be reliably assessed. Two studies reported peri-procedure complications of endovascular therapy in a total of 396 patients. There were no deaths, and serious peri-procedure side-effects occurred in <2% of patients.

Conclusion: A meta-analysis of 8 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 are needed to definitively determine whether CCSVI is more frequent in patients with MS and those without MS.

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 MS¹. 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 MS²⁻¹¹. 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. The main focus of this first report is to describe and systematically review this 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 CCSVI¹². 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 MS⁴. 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. Since none have yet been published, this report will not comment about the potential benefits of endovascular therapy for MS.

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

METHODS

a) Literature searches

For this first report, 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 present), the Cochrane Central Register of Controlled Trials (2005 to present) and EMBASE (2005 to present). 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

In order to be eligible for this systematic review, studies of association had to meet all of the following criteria: reporting of original data in a peer-reviewed publication; use of at least one of Doppler ultrasonography, magnetic resonance venography, or CT 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.

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

No randomized trials have been published about the benefits and harms of endovascular therapy. Therefore, we focused on the harms of endovascular therapy, and identified all studies that reported original data in more than 10 patients with MS.

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. Inter-rater reliability was assessed using the kappa statistic – the values of kappa for level 1 screening were 0.73 and 0.72 for the studies of association and the studies of treatment, respectively.

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, and the Cochrane Collaboration's tool for risk of bias assessment for the studies of therapy)^{13,14}. Disagreements were resolved by consensus.

d) Presentation of data

Eight studies that described the association between CCSVI diagnosed by ultrasonography and MS were considered similar enough to allow statistical meta-analysis^{3,15-21}. 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 1: Identification of Studies of Association

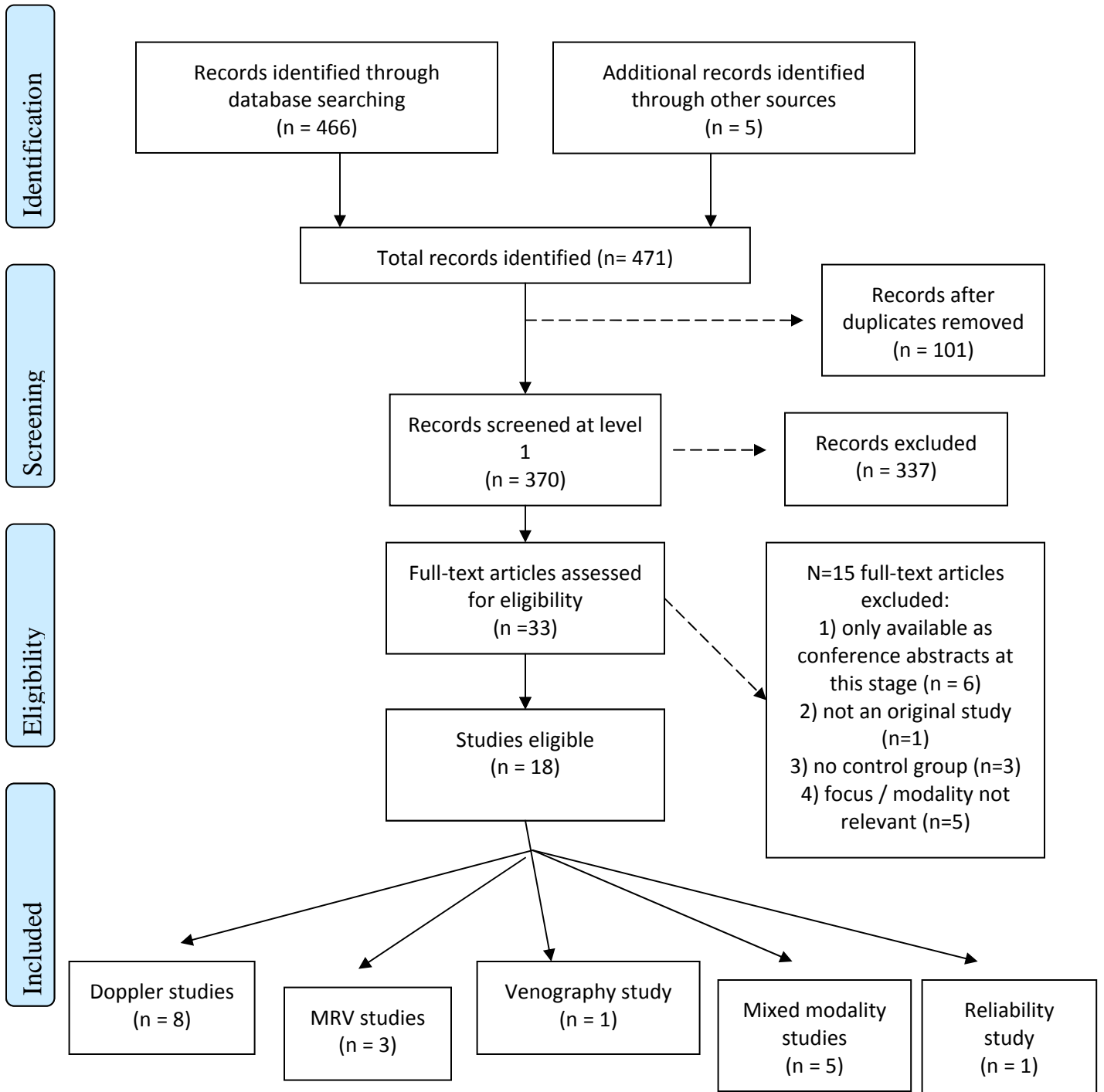
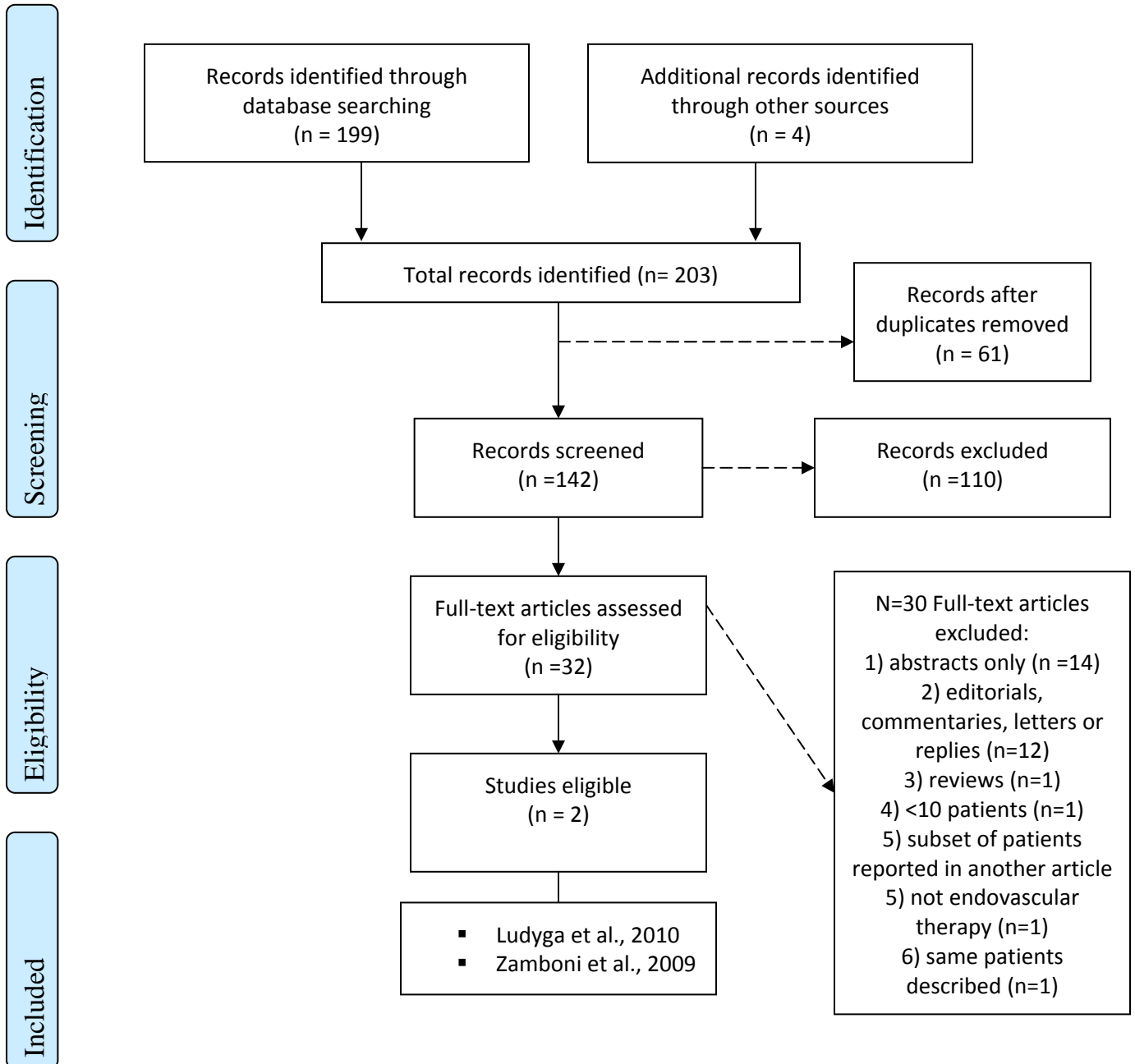


Figure 2: Identification of Studies of Adverse Effects of Endovascular Interventions for CCSVI



II. Descriptions and results of studies of association

A) Studies of Doppler ultrasonography

For more information about the results of the meta-analysis of the eight studies of association that used Doppler ultrasonography, please refer to the CMAJ publication entitled: *Systematic review of the association between chronic cerebrospinal venous insufficiency and multiple sclerosis*, available at: www.cmaj.ca/lookup/doi/10.1503/cmaj.111074. See below for a basic description of each of the eight studies.

a) Description of individual studies that used Doppler ultrasonography

Given the heterogeneity observed in the results of the meta-analysis, we provide brief comments on each of the studies below.

The Zamboni study³ 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 study²¹ 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 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.

Baracchini¹⁶ 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%) OND patients 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. Centonze¹⁷ 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 unblinded¹⁵. 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.

Mayer²⁰ 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.

Doepf's study¹⁸ 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.

Krogias¹⁹ 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.

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 controls²²⁻²⁴, and met our eligibility criteria for inclusion in this systematic review. A second study by Zivadinov²⁵ 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 treatment¹², 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 Hojnacki⁵ because all MS patients had CCSVI diagnosed by ultrasonography, and the study appeared to include the same patients as Zivadinov's study²⁵.

The characteristics of the three eligible studies²²⁻²⁴ 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).

Zivadinov²⁴ 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 controls²³. 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 neck²². 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 \pm 123 mL/min in MS vs 813 \pm 184 mL/min in HC; p=0.07), or normalized IJV flow (70% \pm 21 in MS vs 70% \pm 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.

b) Reproducibility of MRV findings.

Zivadinov studied 6 MS patients and 6 healthy controls one week apart using 2D TOF and 3DTRICKS to assess image-reimage reproducibility²⁴. 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) 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^{5,25}. 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 ultrasonography²⁶. 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.

However, one study from an MS clinic in Lebanon has reported on CV findings in a convenience sample of 42 MS patients²⁷. Their mean age 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.

We identified five studies that reported CV results in patients who were found to have CCSVI on ultrasonography. However, two pairs of studies appeared to report on the same groups of patients: Bartolomei and Zamboni reported on the same 65 patients^{2,9} (we have excluded Bartolomei’s study), and Zivadinov and Hojnacki appear to report on the same 10 MS patients^{5,25} (we have excluded Zivadinov’s study). Thus, below we summarize the results of three studies that reported CV results in MS patients with CCSVI.

Zamboni reported that all 65 MS patients (100%) with CCSVI had significant extracranial venous stenoses². 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 studied⁵. There was a similar lack of technical information about the venographic technique as in Zamboni’s paper². 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 CCSVI¹⁶. 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.

D) 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.

We could not identify any published randomized trials of endovascular therapy for MS. Because of the potential biases of the published non-controlled observational studies, we have decided not to include the results of those studies in this report.

Three randomized trials have been registered with clinicaltrials.gov (<http://clinicaltrials.gov/ct2/results?term=ccsvi>). 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; the Italian study expected to start enrollment in July 2011.

b) 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 three studies of endovascular therapy for MS that reported harms of the procedure^{12,28,29}. One study reported on a subset of patients from a larger study and therefore is not summarized here²⁹.

Zamboni reported on 65 consecutive MS patients with CCSVI¹². Patients underwent venoplasty, and stents were only inserted in a subset of patients. An attempted 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 which 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 CCSVI²⁸. 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 (331) and the number of patients with venoplasty alone and at least one stent (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.

No good studies have been reported describing the long-term complications of endovascular therapy for MS.

c) Re-stenosis after endovascular therapy

Zamboni's protocol called for ultrasonography at 3, 6, 12, 15 and 18 months after initial treatment¹². 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.

DISCUSSION

Studies of Doppler ultrasonography

Although the results of our meta-analysis of eight studies that used Doppler ultrasonography to evaluate the frequency of chronic cerebrospinal venous insufficiency in patients with MS relative to healthy controls demonstrate a strong, statistically significant association between CCSVI and multiple sclerosis, the large amount of heterogeneity between the individual studies' results do not allow definitive conclusions to be drawn. For further details about the meta-analysis, please refer to the CMAJ publication entitled: *Systematic review of the association between chronic cerebrospinal venous insufficiency and multiple sclerosis*, available at: www.cmaj.ca/lookup/doi/10.1503/cmaj.111074.

Studies of magnetic resonance venography

Only three studies assessing MRV in MS patients and non-MS controls met our inclusion criteria. 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.

One 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 abnormality²⁵. This study needs to be replicated in other centres with larger sample sizes.

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.

We also note that the intra-rater agreement for TOF and TRICKS MRV reported by Zivadinov was moderate to poor²⁴.

One high quality but relatively small study reported venographic findings in a relatively unselected group of MS patients²⁷. 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.

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

Only two studies have reported the frequency of short-term complications of endovascular therapy, in 65 and 331 patients. No deaths were reported. Post-intervention bleeding, stent thrombosis (with no important clinical consequences) and transient atrial fibrillation were reported, but all occurred in less than 2% of patients. Thus, despite rare reports of death after endovascular interventions, the frequency of severe side-effects appears low. Stents are associated with a risk of stent migration, and presumably a higher frequency of major bleeding because of the more intense and longer use of anti-thrombotic therapy. However, the magnitude of the excess risks associated with stent insertion compared to venoplasty alone is not known.

FINAL SUMMARY

A meta-analysis of 8 studies found a positive association between chronic cerebrospinal venous insufficiency in multiple sclerosis patients compared to healthy controls that was statistically significant, even when a “conservative” analysis was conducted. However, there was marked heterogeneity among studies, which we are unable to explain. As well, concern remains about the success of blinding in this highly operator-dependent technique. Thus, definitive conclusions cannot be drawn at this time.

Although the ultrasound techniques used in these studies appear to have been similar, with some of the investigators having been trained by Zamboni, it is possible that some of the heterogeneity was caused by differences in ultrasound techniques and protocols. Therefore, it is important that ultrasonographers agree upon the technique that should be used to diagnose CCSVI. Further studies of large numbers of patients, with careful blinding of ultrasonographers who use a standardized technique, are awaited with interest.

Unfortunately, the current literature about MRV in MS does not allow any firm conclusions to be reached about the frequency of MRV abnormalities in MS patients and those without MS, or the correlation between MRV and ultrasound when assessing the IJV.

Only one small venographic study has been conducted in relatively unselected patients with MS, and it did not study patients without MS. It found stenosis in the extracranial veins in only 9% of patients with clinically isolated syndrome, but found stenosis in 85% of patients who had MS for an average of 14 years. Few studies reported the results of contrast venography in MS patients with CCSVI and they reported different results.

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Table 1. 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 ²² . <i>Funding:</i> unknown	Umea, Sweden	MS clinic	MRI 3T Philips, 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 ²³ . <i>Funding:</i> 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 PC 1.4mm venc 15cm/s – 3d CEMRA 3mm – 2d PC perpendicular to ICV/SS	Blinded	Convenience sample

			(blinded reader) – Only assessed ICV, StrS – Cardiac gated		
Zivadinov, R., et al., 2011 ²⁴ . <i>Funding:</i> unknown	Buffalo, NY, USA	MS clinic	3T MRI, 8 channel – 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	MR image interpreters blinded, not sure about those who conducted the test	Consecutive patients

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

STUDY: 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.										
Notes											
STUDY: 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, CI to MRI, allergic reaction to dye, impaired renal function.										
Notes	Controls: age- and sex-matched with MS patients.										
STUDY: 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, CI to contrast, pregnancy, conditions known to be associated with pathological abnormalities of the neck.								
Notes	Controls: age- and sex-matched with MS patients.								

Abbreviations:

RR = relapse-remitting MS

PP = primary progressive MS

SP = secondary progressive MS

OND = other neurological diseases

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)